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Pharmaceutical Process Scale-Up

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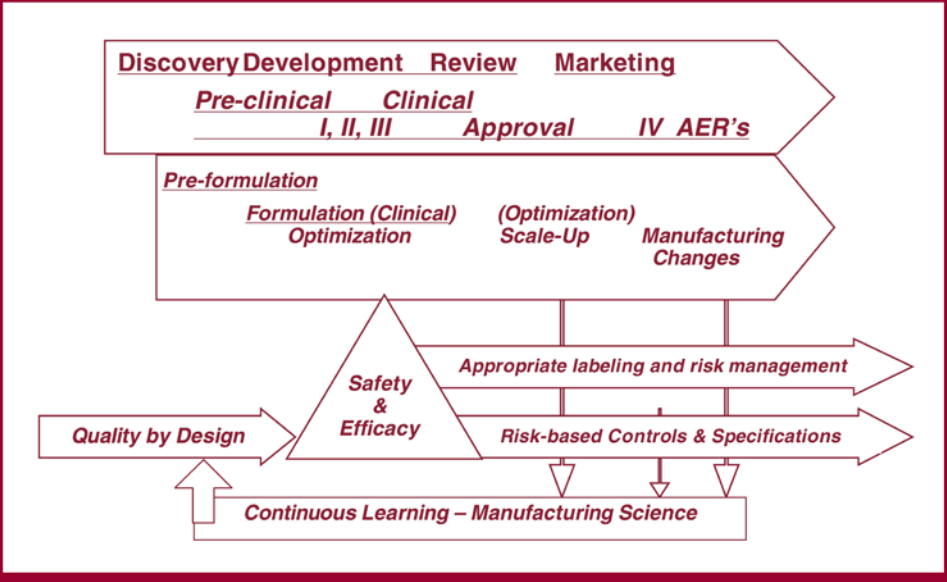

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Pharmaceutical Process Scale-Up

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To my wife, Sonia,
my children, Hanna, Daniela, Ilan, Emanuel, and Maya,
and to the memory of my parents.

Introduction

Scale-up is generally defined as the process of increasing batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume.

In mixing applications, scale-up is indeed concerned with increasing the linear dimensions from the laboratory to the plant size. On the other hand, processes exist (e.g., tableting) where the term "scale-up" simply means enlarging the output by increasing the speed. To complete the picture, one should point out special procedures (especially in biotechnology) where an increase of the scale is counterproductive and "scale-down" is required to improve the quality of the product.

In moving from research and development (R&D) to production scale, it is sometimes essential to have an intermediate batch scale. This is achieved at the so-called pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. This scale also makes it possible to produce enough product for clinical testing and to manufacture samples for marketing. However, inserting an intermediate step between R&D and production scales does not, in itself, guarantee a smooth transition. A well-defined process may generate a perfect product both in the laboratory and the pilot plant and then fail quality assurance tests in production.

Imagine that you have successfully scaled up a mixing or a granulating process from a 10-liter batch to a 75-liter and then to a 300-liter batch. What exactly happened? You may say, "I got lucky." Apart from luck, there had to be some physical similarity in the processing of the batches. Once you understand what makes these processes similar, you can eliminate many scale-up problems.

A rational approach to scale-up has been used in physical sciences, viz., fluid dynamics and chemical engineering, for quite some time. This approach is based on process similarities between different scales and employ dimensional analysis that was developed a century ago and has since gained wide recognition in many industries, especially in chemical engineering (1).

Dimensional analysis is a method for producing dimensionless numbers that completely characterize the process. The analysis can be applied even when the equations governing the process are not known. According to the theory of models, two processes may be considered completely similar if they take place in similar geometrical space and if all the dimensionless numbers necessary to describe the process have the same numerical value (2).

The scale-up procedure, then, is simple: express the process using a complete set of dimensionless numbers, and try to match them at different scales. This dimensionless space in which the measurements are presented or measured will make the process scale invariant.

Dimensionless numbers, such as Reynolds and Froude numbers, are frequently used to describe mixing processes. Chemical engineers are routinely concerned with problems of water–air or fluid mixing in vessels equipped with turbine stirrers where scale-up factors can be up to 1:70 (3). This approach has been applied to pharmaceutical granulation since the early work of Hans Leuenberger in 1982 (4).

One way to eliminate potential scale-up problems is to develop formulations that are very robust with respect to processing conditions. A comprehensive database of excipients detailing their material properties may be indispensable for this purpose. However, in practical terms, this cannot be achieved without some means of testing in production environment and, since the initial drug substance is usually available in small quantities, some form of simulation is required on a small scale.

In tableting applications, the process scale-up involves different speeds of production in what is essentially the same unit volume (die cavity in which the compaction takes place). Thus one of the conditions of the theory of models (similar geometric space) is met. However, there are still kinematic and dynamic parameters that need to be investigated and matched for any process transfer. One of the main practical questions facing tablet formulators during development and scale-up is this: Will a particular formulation sustain the required high rate of compression force application in a production press without lamination or capping? Usually, such questions are never answered with sufficient credibility, especially when only a small amount of material is available and any trial and error approach may result in costly mistakes along the scale-up path.

As tablet formulations are moved from small-scale research presses to high-speed machines, potential scale-up problems can be eliminated by simulation of production conditions in the formulation development lab. In any process transfer from one tablet press to another, one may aim to

preserve mechanical properties of a tablet (density and, by extension, energy used to obtain it) as well as its bio-availability (e.g., dissolution that may be affected by porosity). A scientifically sound approach would be to use the results of the dimensional analysis to model a particular production environment. Studies done on a class of equipment generally known as compaction simulators or tablet press replicators can be designed to facilitate the scale-up of tableting process by matching several major factors, such as compression force and rate of its application (punch velocity and displacement), in their dimensionless equivalent form.

Any significant change in the process of making a pharmaceutical dosage form is subject to regulatory concern. Scale-Up and Postapproval Changes (SUPAC) are of special interest to the Food and Drug Administration (FDA) as is evidenced by a growing number of regulatory documents released in the last several years by the Center for Drug Evaluation and Research (CDER), including Immediate Release Solid Oral Dosage Forms (SUPAC-IR), Modified Release Solid Oral Dosage Forms (SUPAC-MR), and Semisolid Dosage Forms (SUPAC-SS). Additional SUPAC guidance documents being developed include Transdermal Delivery Systems (SUPAC-TDS), Bulk Actives (BACPAC), and Sterile Aqueous Solutions (PAC-SAS). Collaboration between the FDA, pharmaceutical industry, and academia in this and other areas has recently been launched under the framework of the Product Quality Research Institute (PQRI).

Scale-up problems may require postapproval changes that affect formulation composition, site change, and manufacturing process or equipment changes (by the way, from the regulatory standpoint, scale-up and scale-down are treated with the same degree of scrutiny). In a typical drug development cycle, once a set of clinical studies have been completed or New Drug Application (NDA)/Abbreviated New Drug Application (ANDA) has been approved, it becomes very difficult to change the product or the process to accommodate specific production needs. Such needs may include changes in batch size and manufacturing equipment or process.

Post-approval changes in the size of a batch from the pilot scale to larger or smaller production scales call for submission of additional information in the application, with the specific requirement that the new batches are to be produced using similar test equipment and in full compliance with Current Good Manufacturing Practice (cGMP) and the existing Standard Operating Procedures (SOPs). Manufacturing changes may require new stability, dissolution, and in vivo bioequivalence testing. This is especially true for Level 2 equipment changes (change in equipment to a different design and different operating principles), Level 2 process changes (including changes such as mixing times and operating speeds within application/validation ranges) and Level 3 changes (change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder).

Any such testing and accompanying documentation are subject to FDA approval and can be very costly. In 1977, the FDA's Office of Planning and Evaluation (OPE) undertook a study of the impact of SUPAC guidance on cost savings to the industry. The findings indicated that SUPAC guidance generated substantial savings to the industry because it permitted, among other factors, shorter waiting times for site transfers, more rapid implementation of process and equipment changes, as well as batch size increases and reduction of quality control costs.

In early development stages of a new drug substance, relatively little information is available regarding its polymorphic forms, solubility, etc. As the final formulation is developed, changes to the manufacturing process may change the purity profile or physical characteristics of the drug substance and thus cause batch failures and other problems with the finished dosage form.

FDA inspectors are instructed to look for any differences between the process filed in the application and the process used to manufacturer the bio/clinical batch. Furthermore, one of the main requirements of a manufacturing process is that the process will yield a product that is equivalent to the substance on which the biostudy or pivotal clinical study was conducted. Validation of the process development and scale-up should include sufficient documentation so that a link between the bio/clinical batches and the commercial process can be established. If the process is different after scale-up, the company has to demonstrate that the product produced by a modified process will be equivalent, using data such as granulation studies, finished product test results, and dissolution profiles.

Many of the FDA's post-approval, pre-marketing inspections result in citations because validation (and consistency) of the full-scale batches could not be established due to problems with product dissolution, content uniformity, and potency. Validation reports on batch scale-ups may also reflect selective reporting of data.

Of practical importance are the issues associated with a technology transfer in a global market. Equipment standardization inevitably will cause a variety of engineering and process optimization concerns that, generally speaking, can be classified as SUPAC.

To summarize, the significant aspects of pharmaceutical scale-up are presented in this book in order to illustrate potential concerns, theoretical considerations, and practical solutions based on the experience of the contributing authors. In no way do we claim a comprehensive treatment of the subject. A prudent reader may use this handbook as a reference and an initial resource for further study of the scale-up issues.

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Preface

This book deals with a subject that is both fascinating and vitally important for the pharmaceutical industry—the procedures of transferring the results of research and development (R&D) obtained on laboratory scale to the pilot plant and finally to production scale.

Although some theory and history of process scale-up is presented in several chapters, the general reader is not expected to possess special knowledge of physics or engineering since any theoretical considerations are fully explained.

The primary objective of this volume, however, is to provide insight into the practical aspects of process scale-up. As a source of information on batch enlargement techniques, this book will be of practical interest to formulators, process engineers, validation specialists, and quality assurance personnel, as well as production managers. It will also provide interesting reading material for anyone involved in Process Analytical Technology (PAT), technology transfer, and product globalization.

The regulatory aspects of scale-up and post-approval changes are addressed in detail throughout the book and in a separate chapter. A diligent attempt was made to keep all references to the Food and Drug Administration (FDA) regulations as complete and current as possible.

The process of scale-up in the pharmaceutical industry generally involves moving a product from research and development into production. Numerous pitfalls could be met on this path. It is a well-known fact that often the production process cannot achieve the same product quality as was envisioned in the development and pre-approval stages. Losses in terms of effort and money can be enormous, which is why scale-up and post-approval changes are so important and so strictly regulated.

This volume is designed to provide some answers that can facilitate the scale-up process. The main underlying theme that can be detected in almost every chapter of the book is reference to dimensional analysis, a

theoretical approach that makes it possible to describe any unit operation (in fact, any process) in terms of dimensionless variables. Once this mathematical model is achieved, the process becomes "scale invariable," that is, independent of scale. In other words, the key to successful scale-up is to eliminate the scale (linear dimensions, time, etc.) from your process description.

What sounds good in theory may be very difficult to achieve in practice, of course, and not only because theoretical modeling is just that—a model, an approximation of reality. There are always some practical "trade secrets" that are known to experienced operators and the experts in the field and that do not necessarily emerge from any academic discussion. These hands-on recommendations and advice are given a prominent place in this book along with theoretical considerations.

Since the publication of a very successful First Edition of *Pharmaceutical Process Scale-Up*, several crucial related FDA documents have been revised. Also, significant new FDA initiative the (the aforementioned Process Analytical Technology or PAT), has had a strong impact on the pharmaceutical industry.

PAT Guidance, listed in the Appendix to this book, has a clear implication for scientific approach to scale-up. To quote:

> Structured product and process development on a small scale, using experiment design and an on- or in-line process analyzer to collect data in real time for evaluation of kinetics on reactions and other processes such as crystallization and powder blending can provide valuable insight and understanding for process optimization, scale-up, and technology transfer. Process understanding then continues in the production phase when possibly other variables (e.g., environmental and supplier changes) may be encountered.[a]

Scale-up studies are referred to as one of the primary sources of data and information needed to understand the "multifactorial relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls)".[a] Using small-scale equipment (to eliminate certain scale-up issues) in continuous processing is considered to be one of the ways to achieve the declared PAT goal "to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process".[a] Experts in the field (from both the FDA and the industry) started talking about a "Make Your Own SUPAC" concept (alternatively called PAT-SUPAC or SUPAC-C). Indeed, if the new technology can provide better process understanding and

[a] Guidance for Industry: PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. Guidance for Industry, FDA, September 2004.

risk management, then perhaps the resultant improved quality assurance during post-approval changes should provide some regulatory relief.[b]

In addition to readjusting the focus of this book to show the importance of the PAT initiative for pharmaceutical process scale-up, there have been several major revisions and additions.

Most of the chapters have been updated to reflect the increased body of knowledge in the respective areas of unit operations. The sections on scale-up of granulation and tableting have been completely revised. New sections have been added, namely, on the scale-up of roller compaction, extrusion, and hard gelatin encapsulation.

If you are familiar with the First Edition of this book, you are encouraged to peruse this Second Edition because:

- This edition puts special emphasis on "connecting the dots" between SUPAC and PAT guidances (reflecting the new direction that the FDA and the industry are now taking),
- Many chapters underwent a thorough revision based on the rapid change in the state of the art and/or readers' practical suggestions,
- The chapter on compaction and tableting has been completely rewritten to reflect the more comprehensive perspective in both theoretical and practical aspects,
- New chapters on several unit operations (such as encapsulation, extrusion and spheronizing, and roller compaction) have been added.

All in all, this new edition should be a welcome addition to the libraries of pharmaceutical scientists, process engineers, and educators.

[b] Ajaz Hussain. "FDA's Initiative on a Drug Quality System for the 21st Century: "A Once in a Lifetime Opportunity". AAPS Meeting Presentation, October 2003.

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1

Dimensional Analysis and Scale-Up in Theory and Industrial Application

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INTRODUCTION

A chemical engineer is generally concerned with the industrial implementation of processes in which chemical or microbiological conversion of material takes place in conjunction with the transfer of mass, heat, and momentum. These processes are scale-dependent, that is, they behave differently on a small scale (in laboratories or pilot plants) than on a large scale (in production). They include heterogeneous chemical reactions and most unit operations. Understandably, chemical engineers have always wanted to find ways of simulating these processes in models to gain insights that will assist them in designing new industrial plants. Occasionally, they are faced with the same problem for another reason: an industrial facility already exists but will not function properly, if at all, and suitable measurements have to be carried out to discover the cause of the difficulties and provide a solution.

Irrespective of whether the model involved represents a "scale-up" or a "scale-down," certain important questions always apply:

1. How small can the model be? Is one model sufficient or should tests be carried out in models of different sizes?
2. When must or when can physical properties differ? When must the measurements be carried out on the model with the original system of materials?

3. Which rules govern the adaptation of the process parameters in the model measurements to those of the full-scale plant?
4. Is it possible to achieve complete similarity between the processes in the model and those in its full-scale counterpart? If not, how should one proceed?

These questions touch on the fundamentals of the theory of models, which is based on dimensional analysis. Although they have been used in the field of fluid dynamics and heat transfer for more than a century—cars, aircraft, vessels, and heat exchangers were scaled-up according to these principles—these methods have gained only a modest acceptance in chemical engineering. University graduates are usually not skilled enough to deal with such problems at all. On the other hand, there is no motivation for this type of research at universities since, as a rule, they are not confronted with scale-up tasks and are not equipped with the necessary apparatus on the bench scale. All of these reasons give the totally wrong impression that these methods are, at most, of marginal importance in practical chemical engineering, otherwise they would have been taught and dealt with in greater depth.

DIMENSIONAL ANALYSIS

The Fundamental Principle

Dimensional analysis is based on the recognition that a mathematical formulation of a physicotechnological problem can be of general validity only when the process equation is *dimensionally homogenous*, which means that it must be valid in any system of dimensions.

What Is a Dimension?

A dimension is a purely qualitative description of a perception of a physical entity or a natural appearance. A length can be experienced as a height, a depth, or a breadth. A mass presents itself as a light or heavy body and time as a short moment or a long period. The dimension of a length is Length (L), the dimension of a mass is Mass (M), etc.

What Is a Physical Quantity?

Unlike a dimension, a physical quantity represents a quantitative description of a physical quality (e.g., a mass of 5 kg). It consists of a measuring unit and a numerical value. The measuring unit of length can be a meter, a foot, a cubit, a yardstick, a nautical mile, a light year, etc. The measuring units of energy are, for intance, Joule, cal, eV, etc. (It is therefore necessary to establish the measuring units in an appropriate measuring system.)

Table 1 Base Quantities, Their Dimensions and Units According to SI

Base quantity	Base dimension	Base unit
Length	L	m (meter)
Mass	M	kg (kilogram)
Time	T	s (second)
Thermodynamic temperature	Θ	K (Kelvin)
Amount of substance	N	mol (mole)
Electric current	I	A (ampère)
Luminous intensity	I_v	cd (Candela)

Base and Derived Quantities and Dimensional Constants

A distinction is being made between basic and secondary quantities, the latter often referred to as derived quantities. The base quantities are based on standards and are quantified by comparison with these standards.

The secondary units are derived from the primary ones according to physical laws, e.g., velocity = length/time. (The borderline separating both types of quantities is largely arbitrary; for example, 50 years ago a measuring system was used in which force was a primary dimension instead of mass.)

All secondary units must be coherent with the basic units (Table 1), e.g., the measuring unit of velocity must not be miles/hr or km/hr but m/sec.

If a secondary unit has been established by a physical law, it can happen that it contradicts another one. For example: According to Newton's Second Law of Motion, the force F is expressed as a product of mass m and acceleration a, $F = ma$, having the measuring unit of (kg m/sec$^2 \equiv$ N). According to Newton's Law of Gravitation, force is defined by $F \propto m_1 m_2 / r^2$, thus leading to another measuring unit (kg^2/m^2). To remedy this, the gravitational constant G—a dimensional constant—had to be introduced to ensure the dimensional homogeneity of the latter equation, $F = \mathrm{G} m_1 m_2 / r^2$. Another example affects the universal gas constant R, the introduction of which ensures that in the perfect gas equation of state $pV = n\mathrm{RT}$, the secondary unit for work $W = pV$ [M L^2 T^{-2}] is not contradicted.

Another class of derived quantities is represented by the coefficients in diverse physical equations, e.g., transfer equations. They are established by the respective equations and determined via measurement of their constituents (e.g., heat and mass transfer coefficients).

Dimensional Systems

A dimensional system consists of all the primary and secondary dimensions and corresponding measuring units. The currently used International System

Table 2 Often Used Physical Quantities and Their Dimensions According to the Currently Used SI in Mechanical and Thermal Problems

Physical quantity	Dimension
Angular velocity, shear rate, frequency mass transfer coefficient $k_L a$	T^{-1}
Velocity	$L\ T^{-1}$
Acceleration	$L\ T^{-2}$
Kinematic viscosity, diffusion coefficient, thermal diffusivity	$L^2\ T^{-1}$
Density	$M\ L^{-3}$
Surface tension	$M\ T^{-2}$
Dynamic viscosity	$M\ L^{-1}\ T^{-1}$
Momentum	$M\ L\ T^{-1}$
Force	$M\ L\ T^{-2}$
Pressure, stress	$M\ L^{-1}\ T^{-2}$
Angular momentum	$M\ L^2\ T^{-1}$
Energy, work, torque	$M\ L^2\ T^{-2}$
Power	$M\ L^2\ T^{-3}$
Heat capacity	$L^2\ T^{-2}\ \Theta^{-1}$
Thermal conductivity	$M\ L\ T^{-3}\ \Theta^{-1}$
Heat transfer coefficient	$M\ T^{-3}\ \Theta^{-1}$

of Dimensions (''Système International d'unités,'' SI) is based on seven basic dimensions. They are presented in Table 1, together with their corresponding basic units. For some of them, a few explanatory remarks may be necessary.

Temperature expresses the thermal level of a system and not its energy content. (A fivefold mass of a matter has fivefold thermal energy at the same temperature.) The thermal energy of a system can indeed be converted into the mechanical energy (base unit Joule). Moles are amounts of matter and must not be confused with the quantity of mass. Molecules react as individual entities regardless of their mass: one mole of hydrogen (2 g/mol) reacts with one mole of chlorine (71 g/mol) to produce two moles of hydrochloric acid, HCl.

Table 2 shows the most important secondary dimensions. Table 3 refers to some very frequently used secondary units that have been named after famous researchers.

Dimensional Homogeneity of Physical Content

The aim of dimensional analysis is to check whether the physical content under examination can be formulated in a dimensionally homogeneous manner or not. The procedure necessary to accomplish this consists of two parts:

Table 3 Important Secondary Measuring Units in the Mechanics, Named After Famous Researchers

Secondary quantity	Dimension	Measuring unit	Abbreviation
Force	$M\ L\ T^{-2}$	$kg\ m/sec^2 \equiv N$	Newton
Pressure	$M\ L^{-1}\ T^{-2}$	$kg/m/sec^2 \equiv Pa$	Pascal
Energy	$M\ L^2\ T^{-2}$	$kg\ m^2/sec^2 \equiv J$	Joule
Power	$M\ L^2\ T^{-3}$	$kg\ m^2/sec^3 \equiv W$	Watt

1. First, all physical parameters necessary to describe the problem are listed. This so-called "relevance list" of the problem consists of the quantity in question and of all the parameters that influence it. In each case, only *one* target quantity must be considered; it is the only dependent variable. On the other hand, all the influencing parameters must be primarily independent of each other.
2. In the second step, the dimensional homogeneity of the physical content is checked by transferring it in a dimensionless form. *Note*: A physical content that can be transformed in dimensionless expressions is dimensionally homogeneous.

The information given hitherto will be made clear by an amusing but instructive example:

Example 1: What Is the Correlation Between the Baking Time and the Weight of a Christmas Turkey?

We first recall the physical situation; to facilitate this, we draw a sketch (see Fig. 1). At high oven temperatures, the heat is transferred from the heating elements to the meat surface by both radiation and heat convection. From there, it is transferred solely by the unsteady-state heat conduction that surely represents the rate-limiting step of the whole heating process (Fig. 1).

The higher the thermal conductivity λ of the body, the faster the heat spreads out. The higher its volume-related heat capacity ρC_p, the slower the heat transfer. Therefore, unsteady-state heat conduction is characterized by only one material property, the thermal diffusivity, $a \equiv \lambda/\rho C_p$ of the body.

Baking is an endothermal process. The meat is cooked when a certain temperature distribution (T) is reached. It's about the time θ necessary to achieve this temperature field.

After these considerations we are able to precisely make the relevance list:

$$\{\theta, A, a, T_0, T\} \tag{1}$$

The base dimension of temperature Θ appears only in two parameters. They can, therefore, produce only one dimensionless quantity:

$$\Pi_1 \equiv T/T_0 \quad \text{or} \quad (T_0 - T)/T_0 \tag{2}$$

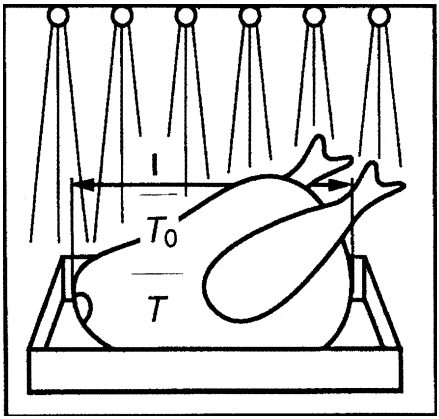

Figure 1 Sketch of the oven with piece of poultry.

The residual three quantities form one additional dimensionless number:

$$\Pi_2 \equiv a\theta/A \equiv \mathrm{Fo} \tag{3}$$

In the theory of heat transfer, Π_2 is known as the Fourier number. Therefore, the baking procedure can be presented in a two-dimensional frame:

$$T/T_0 = f(\mathrm{Fo}) \tag{4}$$

Here, five dimensional quantities [Eq. (1)] produce two dimensionless numbers [Eq. (4)]. This had to be expected because the dimensions in question are comprised of three basic dimensions: $5-3=2$ (see the discussion on pi theorem later in this chapter).

We can now easily answer the question concerning the *correlation between the baking time and the weight of the Christmas turkey*, without explicitly knowing the function f, which connects both numbers [Eq. (4)]. To achieve the same temperature distribution T/T_0 or $(T_0-T)/T_0$ in differently sized bodies, the dimensionless quantity $a\theta/A \equiv \mathrm{Fo}$ must have the same (=idem) numerical value. Due to the fact that the thermal diffusivity a remains unaltered in the meat of same kind ($a = \mathrm{idem}$), this demand leads to

$$T/T_0 = \mathrm{idem} \rightarrow \mathrm{Fo} \equiv a\theta/A = \mathrm{idem} \rightarrow \theta/A = \mathrm{idem} \rightarrow \theta \propto Ae \tag{5}$$

This statement is obviously useless as a scale-up rule because meat is bought according to weight and not to surface. We can remedy this simply.

In geometrically similar bodies, the following correlation between mass m, surface A, and volume V exists:

$$m = \rho V \propto \rho L^3 \propto \rho A^{3/2} \quad (A \propto L^2) \tag{6}$$

Therefore, from $\rho = \text{idem}$ it follows

$$\begin{aligned} &A \propto m^{2/3} \qquad \text{and by this} \\ &\theta \propto A \propto m^{2/3} \;\rightarrow\; \theta_2/\theta_1 \propto (m_2/m_1)^{2/3} \end{aligned} \tag{7}$$

This is the scale-up rule for baking or cooking time in cases involving meat of the same kind (a, $\rho = \text{idem}$). It states that when the mass of meat is doubled, the cooking time will increase by $2^{2/3} = 1.58$.

West (1) refers to (inferior) cookbooks, which simply say something like "20 minutes per pound," implying a linear relationship with weight. However, there exist superior cookbooks, such as the *Better Homes and Gardens Cookbook* (Des Moines Meredith Corp. 1962), that recognize the non-linear nature of this relationship. The graphical representation of measurements in this book confirms the relationship

$$\theta \propto m^{0.6} \tag{8}$$

which is very close to the theoretical evaluation giving $\theta \propto m^{2/3} = m^{0.67}$.

The elegant solution of this first example should not tempt the reader to believe that dimensional analysis can be used to solve every problem. To treat this example by dimensional analysis, the physics of unsteady-state heat conduction had to be understood. Bridgman's (2) comment on this situation is particularly appropriate:

> The problem cannot be solved by the philosopher in his armchair, but the knowledge involved was gathered only by someone at some time soiling his hands with direct contact.

This transparent and easy example clearly shows how dimensional analysis deals with specific problems and what conclusions it allows. It should now be easier to understand Lord Rayleigh's sarcastic comment with which he began his short essay on "The Principle of Similitude" (3):

> I have often been impressed by the scanty attention paid even by original workers in physics to the great principle of similitude. It happens not infrequently that results in the form of "laws" are put forward as novelties on the basis of elaborate experiments, which might have been predicted a priori after a few minute's consideration.

From the above example, we also learn that transformation of physical dependency from a dimensional into a dimensionless form is automatically accompanied by an essential *compression* of the statement: the set of the dimensionless numbers is smaller than the set of the quantities contained in them, but it describes the problem equally comprehensively. In the above example, the dependency between five dimensional parameters is reduced to a dependency between only two dimensionless numbers. This is the proof of the so-called pi theorem (pi after Π, the sign used for products), which states:

Every physical relationship between n *physical quantities can be reduced to a relationship between* $m = n - r$ *mutually independent dimensionless groups, whereby* r *stands for the rank of the dimensional matrix, made up of the physical quantities in question and generally equal to the number of the basic quantities contained in them.*[*]

DETERMINATION OF A PI SET BY MATRIX CALCULATION

Establishment of a Relevance List of a Problem

As a rule, more than two dimensionless numbers will be necessary to describe a physicotechnological problem and therefore they cannot be derived by the method described above. In this case, the easy and transparent matrix calculation introduced by Pawlowski (6) is increasingly used. It will be demonstrated by the following example. It treats an important problem in industrial chemistry and biotechnology because the gas liquid–contact in mixing vessels belongs to frequently used mixing operations (Fig. 2).

Example 2: The Determination of the Pi Set for the Stirrer Power in the Contact Between Gas and Liquid

We examine the power consumption of a turbine stirrer, the so-called Rushton turbine (inset in Fig. 3, p.12) installed in a baffled vessel and supplied by gas from below.

We facilitate the procedure by systematically listing the target quantity and all the parameters influencing it:

1. Target quantity: mixing power, P
2. Influencing parameters
   a. geometrical: stirrer diameter, d
   b. physical properties
      - fluid density, ρ
      - kinematics viscosity, ν
   c. process related
      - stirrer speed, n
      - gas throughput, q
      - gravitational acceleration, g

[*] The pi theorem is often associated with the name of Buckingham (4), because he introduced this term in 1914, but the proof of it was accomplished in the course of a mathematical analysis of partial differential equations by Federmann in 1911; see Ref. 5, Chap. 1.1, A Brief Historical Survey.

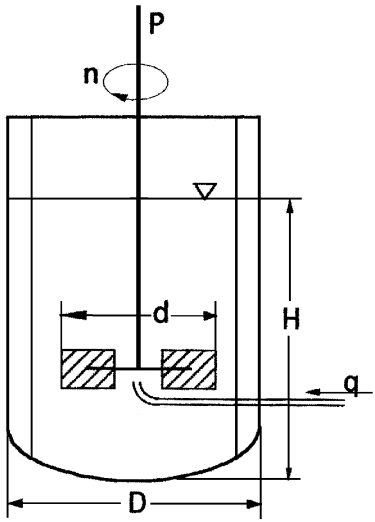

Figure 2 Sketch of the mixing vessel.

The relevance list reads:

$$\{P; d; \rho, v; n, q, g\} \tag{9}$$

We interrupt the procedure by asking some important questions concerning:

a. determination of the characteristic geometric parameter
b. setting of all relevant material properties
c. taking into account the gravitational acceleration

Determination of the Characteristic Geometric Parameter

It is obvious that we could name all the geometric parameters indicated in the sketch. They were all the geometric parameters of the stirrer and of the vessel, especially its diameter D and the liquid height H. In cases of complex geometry, such a procedure would compulsorily deflect from the problem. It is therefore advisable to introduce only one characteristic geometric parameter, knowing that all the others can be transformed into dimensionless geometric numbers by division with this one.

The stirrer diameter was introduced as the characteristic geometric parameter in the above case. This is reasonable. One can imagine how the mixing power would react to an increase of the vessel diameter D: it is obvious that from a certain D on, there would be no influence but a small change of the stirrer diameter d would always have an impact.

Setting of All Relevant Material Properties

In the above relevance list, only the density and the viscosity of the liquid were introduced. The material properties of the gas are of no importance as compared to the physical properties of the liquid. It was also ascertained by measurement that the interfacial tension σ does not affect the stirrer power. Furthermore, measurements revealed that the coalescence behavior of the material system is not affected if aqueous glycerol or cane syrup mixtures are used to increase viscosity in model experiments (7).

The Importance of the Gravitational Constant

Due to the extreme density difference between gas and liquid (approximately 1:1.000), it must be expected that the gravitational acceleration g will exert big influence. One should actually write $g\Delta\rho$ but, since $\Delta\rho = \rho_L - \rho_G \approx \rho_L$, the dimensionless number would contain $g\Delta\rho/\rho_L \approx g\,\rho_L/\rho_L = g$.

We now proceed to solve Example 2.

Constructing and Solving a Dimensional Matrix

In transforming the relevance list Eq. (9) of the above seven physical quantities into a dimensional matrix, the following should be kept in mind to minimize the calculations required:

a. The dimensional matrix consists of a square-core matrix and a residual matrix.
b. The rows of the matrix are formed of basic dimensions contained in the dimensions of the quantities, and they determine the rank r of the matrix. The columns of the matrix are presented by the physical quantities or parameters.
c. Quantities of the square core matrix may eventually appear in all of the dimensionless numbers as "fillers", whereas each element of the residual matrix will appear only in one dimensionless number. For this reason, the residual matrix should be loaded with essential variables such as the target quantity and the most important physical properties and process-related parameters.
d. By the extremely easy matrix rearrangement (linear transformations), the core matrix is transformed into a matrix of unity: the main diagonal consists only of ones and the remaining ô-elements are all zeroes. One should therefore arrange the quantities in the core matrix in a way to facilitate this procedure.
e. After the generation of the matrix of unity, the dimensionless numbers are created as follows: each element of the residual matrix forms the numerator of a fraction, while its denominator consists of the fillers from the matrix of unity with the exponents indicated in the residual matrix.

Let us return to our Example 2. The dimensional matrix reads:

	ρ	d	n	P	v	q	g
Mass (M)	1	0	0	1	0	0	0
Length (L)	−3	1	0	2	2	3	1
Time (T)	0	0	−1	−3	−1	−1	−2
	Core matrix			Residual matrix			

Only one linear transformation is necessary to transform −3 in L-row/ρ-column into zero. The subsequent multiplication of the T-row by −1 transfers −1 to 1:

	ρ	d	n	P	v	q	g
M	1	0	0	1	0	0	0
3M + L	0	1	0	5	2	3	1
−T	0	0	1	3	1	1	2
	Unity matrix			Residual matrix			

The residual matrix contains four parameters; therefore, four Π numbers result:

$$\Pi_1 = \frac{P}{\rho^1 n^3 d^5} = \frac{P}{\rho n^3 d^5} = \text{Ne (Newton number)}$$

$$\Pi_2 = \frac{\nu}{\rho^0 n^1 d^2} = \frac{\nu}{n d^2} = \text{Re}^{-1} \text{ (Reynolds number)}$$

$$\Pi_3 = \frac{q}{d^3 n} = Q \text{ (Gas throughput number)}$$

$$\Pi_4 = \frac{g}{d n^2} = \text{Fr}^{-1} \text{ (Froude number)}$$

The interdependence of seven-dimensional quantities of the relevance list, Equation (9), reduces to a set of only $7 - 3 = 4$ dimensionless numbers,

$$\{\text{Ne}, \text{Re}, Q, \text{Fr}\} \quad \text{or} \quad f(\text{Ne}, \text{Re}, Q, \text{Fr}) = 0 \tag{10}$$

thus again confirming the pi theorem.

Determination of the Process Characteristics

Functional dependency, Equation (10), is the maximum that dimensional analysis can offer here. It cannot provide any information about the form of the function f. This can be accomplished solely by experiments.

The first question we must ask is: Are laboratory tests, performed in one single piece of laboratory apparatus—i.e., on one single scale—capable of providing binding information on the decisive process number? The

answer here is affirmative. We can change Fr by means of the rotational speed of the stirrer, Q by means of the gas throughput, and Re by means of the liquid viscosity independently of each other.

The results of these model experiments are described in detail in Reference 7. For our consideration, it is sufficient to present only the main result here. This states that, in the industrially interesting range ($Re \geq 10^4$ and $Fr \geq 0.65$), the power number Ne is dependent only on the gas throughput number Q. When the gas throughput number Q is increased thus enhancing gas hold-up in the liquid, the liquid density diminishes and Ne decreases to only one-third of its value in non-gassed liquid.

These power characteristics, the analytical expression for which is

$$Ne = 1.5 + (0.5\ Q^{0.075} + 1600\ Q^{2.6})^{-1} \quad (Q \leq 0.15) \tag{11}$$

can be used to reliably design a stirrer drive for the performance of material conversions in gas/liquid systems (e.g., oxidations with O_2 or air, fermentations, etc.) as long as the physical, geometric, and process-related boundary conditions (Re, Fr, and Q) comply with those of the model measurement.

FUNDAMENTALS OF THE THEORY OF MODELS AND OF SCALE-UP

Theory of Models

The results in Figure 3 were acquired by changing the rotational speed of the stirrer and the gas throughput, whereas the liquid properties and the characteristic length (stirrer diameter d) remained constant. But these results could have also been acquired by changing the stirrer diameter: It does not

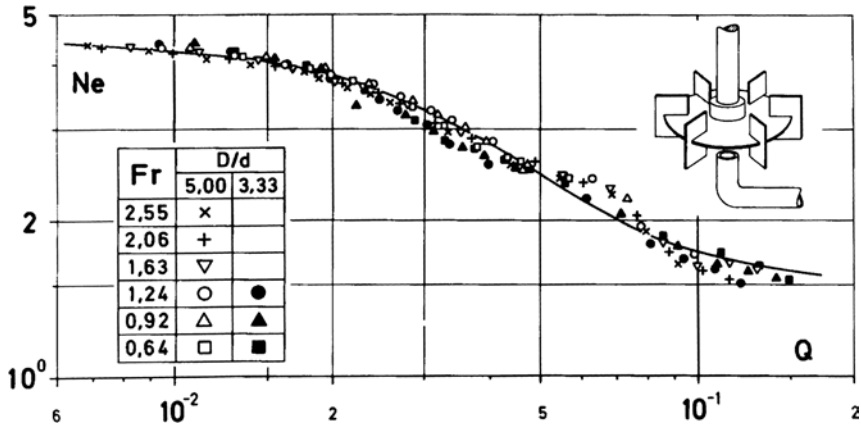

Figure 3 Power characteristics of a turbine stirrer (Rushton turbine) in the range $Re \geq 10^4$ and $Fr \geq 0.65$ for two D/d values. Material system: water/air. *Source*: From Ref. 7.

matter by which means a relevant number (here, Q) is changed because it is dimensionless and therefore independent of scale ("scale invariant"). This fact presents the basis for a reliable scale-up:

> Two processes may be considered completely similar if they take place in similar geometrical space and if all the dimensionless numbers necessary to describe them have the same numerical value (Π_i = identical or idem).

Clearly, the scale-up of a desired process condition from a model to industrial scale can be accomplished reliably only if the problem was formulated and dealt with according to dimensional analysis.

Model Experiments and Scale-Up

In the above example, the process characteristics (here, power characteristics) presenting a comprehensive description of the process were evaluated. This often expensive and time-consuming method is certainly not necessary if one has to only scale-up a given process condition from the model to the industrial plant (or vice versa). With the last example and the assumption that the Ne (Q) characteristics like those in Figure 3 are not explicitely known, the task is to predict the power consumption of a Rushton turbine of $d = 0.8$ m, installed in a baffled vessel of $\mathrm{D} = 4$ m ($\mathrm{D}/d = 5$) and rotating with $n = 200/\mathrm{min}$. The air throughput be $q = 500\,\mathrm{m}^3/\mathrm{hr}$ and the material system is water/air.

One only needs to know—and this is *essential*—that the hydrodynamics in this case are governed solely by the gas throughput number and that the process is described by an unknown dependency Ne (Q). Then one can calculate the Q number of the industrial plant:

$$Q \equiv q/nd^3 = 8.14 \times 10^{-2}$$

What will the power consumption of the turbine be?

Let us assume that we have a geometrically similar laboratory device of $\mathrm{D} = 0.4$ m ($V \approx 0.050\,\mathrm{m}^3$) with a turbine stirrer of $d = 0.08$ m and that the rotational speed of the stirrer is $n = 750/\mathrm{min}$. Which must the gas throughput be to obtain $Q = \mathrm{idem}$ in the laboratory device? The answer is

$$q/nd^3 = 8.14 \times 10^{-2} \rightarrow q = 1.88\ \mathrm{m}^3/\mathrm{hr}$$

Under these conditions, the stirrer power must be measured and the power number $\mathrm{Ne} \equiv P/\rho n^3 d^5$ calculated.

We find $\mathrm{Ne} = 1.75$. Due to the fact that $Q = \mathrm{idem}$ results in $\mathrm{Ne} = \mathrm{idem}$, the power consumption P_T of the industrial stirrer can be obtained:

$$\mathrm{Ne} = \mathrm{idem} \rightarrow \mathrm{Ne_T} = \mathrm{Ne_M} \rightarrow \left(\frac{P}{\rho n^3 d^5}\right)_\mathrm{T} = \left(\frac{P}{\rho n^3 d^5}\right)_\mathrm{M} \tag{12}$$

From $\mathrm{Ne} = 1.75$ found in laboratory measurement, the power P of the industrial turbine stirrer of $d = 0.8\,\mathrm{m}$ and a rotational speed of $n = 200/\mathrm{min}$ is calculated as follows:

$$P = \mathrm{Ne}\,\rho n^3 d^5 = 1.75 \times 1 \times 10^3 \times (200/60)^3 \times 0.8^5 = 21{,}200\,\mathrm{W} \cong 21\,\mathrm{kW}$$

This results in $21/50\,\mathrm{kW/m^3} \approx 0.42\,\mathrm{kW/m^3}$, which is a fair volume-related power input for many conversions in the gas/liquid system.

We realize that in scale-up the comprehensive knowledge of the functional dependency $f(\Pi_i) = 0$ (like that in Fig. 3) is not necessary. All we need to know is which pi space describes the process.

FURTHER PROCEDURES TO ESTABLISH A RELEVANCE LIST

Consideration of the Acceleration Due to Gravity g

If a natural or universal physical constant has an impact on the process, it has to be incorporated into the relevant list, whether it will be altered or not. In this context, the greatest mistakes are made with regard to the gravitational constant g. Lord Rayleigh (3) complained bitterly saying:

> I refer to the manner in which gravity is treated. When the question under consideration depends essentially upon gravity, the symbol of gravity (g) makes no appearance, but when gravity does not enter the question at all, g obtrudes itself conspicuously.

This is all the more surprising in view of the fact that the relevance of this quantity is easy enough to recognize if one asks the following question:

> Would the process function differently if it took place on the moon instead of on Earth?

If the answer to this question is affirmative, g is a relevant variable.

The gravitational acceleration g can be effective solely in connection with the density as gravity $g\rho$. When inertial forces play a role, the density ρ has to be listed additionally. Thus, it follows that:

a. In cases involving the ballistic movement of bodies such as the formation of vortices in stirring, the bow wave of a ship, the movement of a pendulum, and other processes affected by the Earth's gravity, the relevance list comprises $g\rho$ and ρ.
b. Creeping flow in a gravitational field is governed by the gravity $g\rho$ alone.
c. In heterogeneous physical systems with density differences (sedimentation or buoyancy), the difference in gravity $g\Delta\rho$ and ρ play a decisive role.

In Example 2, we have already treated a problem where the gravitational constant is of prime importance due to the extreme difference in

densities in the gas/liquid system, provided that the Froude number is low; ie., Fr < 0.65.

Introduction of Intermediate Quantities

Many engineering problems involve several parameters, that impede the elaboration of the pi space. Fortunately, in some cases, a closer look at a problem (or previous experience) facilitates reduction of the number of physical quantities in the relevance list. This is the case when some relevant variables affect the process by way of a so-called "intermediate" quantity. Assuming that this intermediate variable can be measured experimentally, it should be included in the problem relevance list, if this facilitates the removal of more than one variable from the list.

The impact that the introduction of intermediate quantities can have on the relevance list will be demonstrated in the following elegant example.

Example 3: Mixing Time Characteristics for Liquid Mixtures with Differences in Density and Viscosity

Mixing time θ necessary to achieve a molecular homogeneity of a liquid mixture—normally measured by decolorization methods in material systems *without* differences in density and viscosity depends on only four parameters, stirrer diameter d, density ρ, dynamic viscosity η, and rotational speed n:

$$\{\theta;\, d;\, \rho;\, \nu;\, n\} \tag{13}$$

From this, the mixing time characteristics results to

$$n\theta = f(\mathrm{Re}), \quad \mathrm{Re} \equiv nd^2/\nu \tag{14}$$

See Example 5.2 and Figure 13.

In material systems *with* differences in density and viscosity, the relevance list, Equation (13), enlarges by the physical properties of the second mixing component, by the volume ratio of both phases $\phi = V_2/V_1$, and, due to the density differences, inevitably by the gravity difference $g\Delta\rho$ to nine parameters:

$$\{\theta;\, d;\, \rho_1;\, \nu_1;\, \rho_2;\, \nu_2;\, \phi;\, g\Delta\rho;\, n\} \tag{15}$$

This results in a mixing time characteristics incorporating six numbers:

$$n\theta = f(\mathrm{Re}, \mathrm{Ar},\, \rho_2/\rho_1, \nu_2/\nu_1, \phi) \tag{16}$$

($\mathrm{Re} \equiv nd^2/\nu_1$—Reynolds number, $\mathrm{Ar} \equiv g\Delta\rho d^3/\rho_1{\nu_1}^2$—Archimedes number.)

Meticulous observation of this mixing process (the slow disappearance of the Schlieren patterns as result of the disappearance of density differences), reveals that macromixing is quickly accomplished compared to the micromixing. This time-consuming process already takes place in

a material system that can be fully described by the physical properties of the mixture:

$$\nu^* = f(\nu_1, \nu_2, \phi) \quad \text{and} \quad \rho^* = f(\rho_1, \rho_2, \phi) \tag{17}$$

By introducing these *intermediate* quantities ν^* and ρ^*, the nine-parametric relevance list, Equation (15) reduces by three parameters to a six-parametric one

$$\{\theta; d; \rho^*; \nu^*; g\Delta\rho; n\} \tag{18}$$

and gives a mixing characteristics of only three numbers:

$$n\theta = f(\mathrm{Re}, \mathrm{Ar}) \tag{19}$$

(In this case, Re and Ar have to be formed by ρ^* and ν^*.)

The process characteristics of a crossbeam stirrer was established in this pi space by evaluation of corresponding measurements in two differently sized mixing vessels (D = 0.3 and 0.6 m) using different liquid mixtures ($g\Delta\rho/\rho^* = 0.01$–$0.29$ and $\nu_2/\nu_1 = 1$–5300). It reads (8):

$$\sqrt{n\theta} = 51.6\ \mathrm{Re}^{-1}(\mathrm{Ar}^{1/3} + 3), \quad \mathrm{Re} = 10^1\text{–}10^5, \ \mathrm{Ar} = 10^2\text{–}10^{11} \tag{20}$$

This example clearly shows the big advantages achieved by the introduction of intermediate quantities.

Note: The fluid velocity v in pipes—or the superficial gas velocity v_G in mixing vessels or in bubble columns—presents a well-known process parameter which combines the fluid throughput q and the diameter of the device D: $v \approx q/\mathrm{D}^2$. Nevertheless this parameter is not an intermediate quantity. It cannot replace the diameter of the device; it is simply another expression for the fluid throughput. Reference: The kinematic process numbers like the Reynolds and Froude numbers, which govern the hydrodynamics, necessarily contain the linear dimension of the device.

Material Systems of Unknown Physical Properties

With foams, sludge, and slimes often encountered in biotechnology, we are confronted with the problem of not being able to list the physical properties because they are still unknown and therefore cannot be quantified. This situation often leads to the opinion that dimensional analysis would fail in such cases.

It is obvious that this conclusion is wrong: Dimensional analysis is a *method* based on logical and mathematical fundamentals (2,6). If relevant parameters cannot be listed because they are unknown, one cannot blame the method. The only solution is to perform the model measurements with the same material system and to change the model scales.

Example 4: Scale-Up of a Mechanical Foam Breaker

The question is posed about the mode of performing and evaluating model measurements with a given type of mechanical foam breaker (foam centrifuge, Fig. 4) to obtain reliable information on dimensioning and scale-up of these devices. Preliminary experiments have shown that for each foam emergence—proportional to the gas throughput q_G—for each foam breaker of diameter d, a minimum rotational speed n_{min} exists that is necessary to control it. The dynamic properties of the foam (e.g., density and viscosity, elasticity of the foam lamella, etc.) cannot be fully named or measured. We will have to be content with listing them wholesale as material properties S_i. In our model experiments we will of course be able to replace S_i by the known type of surfactant (foamer) and its concentration c_f (ppm).

In discerning the process parameters we realize that the gravitational acceleration g has no impact on the foam breaking *within* the foam centrifuge: The centrifugal acceleration n^2d exceeds the gravitational one (g) by far. However, we have to recognize that the water content of the foam entering the centrifuge depends very much on the gravitational acceleration.

On the moon the water drainage would be by far less effective. In contrast to the dimensional analysis presented in Reference (9) we are well advised to add g to the relevance list:

$$\{n_{min};\ d;\ \text{type of foamer}, c_f,\ q_G,\ g\} \tag{21}$$

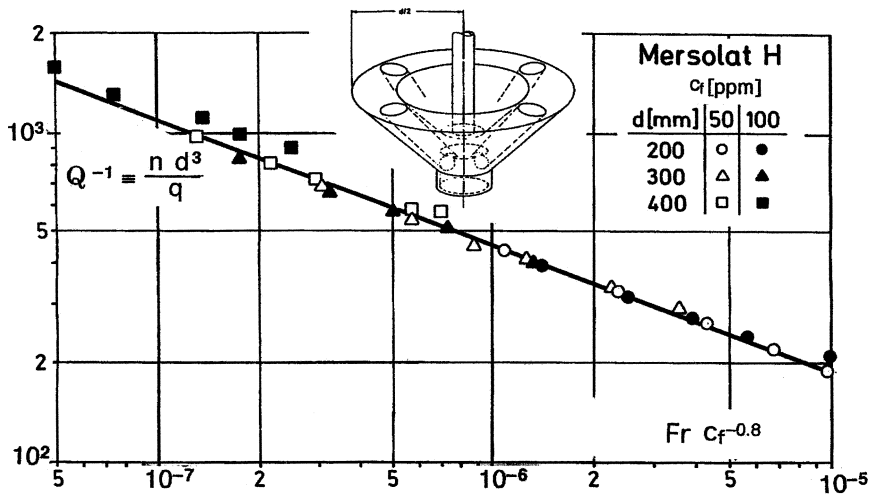

Figure 4 Process characteristics of the foam centrifuge (sketch) for a particular foamer (Mersolat H of Bayer AG, Germany). *Source*: From Ref. 9.

For the sake of simplicity, n_{min} will be replaced by n and q_G by q in the following. For each type of foamer we obtain the following pi space:

$$\left\{\frac{nd^3}{q}, \frac{n^2d}{g}, c_f\right\} \quad \text{or abbreviated} \quad \left\{Q^{-1}, \text{Fr}, c_f\right\} \tag{22}$$

To prove this pi space, measurements in differently sized model equipment are necessary to produce reliable process characteristics. For a particular foamer (Mersolat H of Bayer AG, Germany) the results are given in Figure 4. They fully confirm the pi space, Equation (22).

The straight line in Figure 4 corresponds to the analytic expression

$$Q^{-1} = \text{Fr}^{-0.4} c_f^{0.32} \tag{23}$$

which can be put down to

$$nd = \text{const}\, q^{0.2} f(c_f) \tag{24}$$

Here, the foam breaker will be scaled-up according to its tip speed $u = \pi nd$ in model experiments, which will also moderately depend on the foam yield (q).

In all other foamers examined (9), the correspondence $Q^{-1} \propto \text{Fr}^{-0.45}$ was found. If the correlation

$$Q^{-1} \propto \text{Fr}^{-0.5} f(c_f) \tag{25}$$

proves to be true, then it can be deduced to

$$n^2d/g = \text{const}(c_f) \tag{26}$$

In this case the centrifugal acceleration (n^2d) would present the scale-up criterion and would depend only on the foamer concentration and not on foam yield (q).

Short Summary of the Essentials of Dimensional Analysis and Scale-Up

The advantages made possible by correct and timely use of dimensional analysis are as follows:

1. *Reduction of the number of parameters required to define the problem.* The Π theorem states that a physical problem can always be described in dimensionless terms. This has the advantage that the number of dimensionless groups, which fully describe it, is much smaller than the number of dimensional physical quantities. It is generally equal to the number of physical quantities minus the number of basic units contained in them.

Table 4 Important Named Dimensionless Numbers

Name	Symbol	Group	Remarks
Mechanical unit operations			
Reynolds	Re	vl/ν	$\nu \equiv \mu/\rho$
Froude	Fr	$v^2/(lg)$	
	Fr^*	$v^2\rho/(lg\Delta\rho)$	$\equiv$Fr $(\rho/\Delta\rho)$
Galilei	Ga	gl^3/ν^2	$\equiv Re^2/Fr$
Archmedes	Ar	$g\Delta\rho l^3/\nu^2\rho$	$\equiv$Ga $(\Delta\rho/\rho)$
Euler	Eu	$\Delta p/(\rho v^2)$	
Newton	Ne	$F/(\rho v^2 l^2)$	Force
		$P/(\rho v^3 l^2)$	Power
Weber	We	$\rho v^2 l/\sigma$	
Ohnesorge	Oh	$\eta/(\rho\sigma l)^{1/2}$	$\equiv We^{1/2}/Re$
Mach	Ma	v/v_s	v_s—velocity of sound
Knudsen	Kn	λ_m/l	λ_m—molecular free path length
Thermal unit operations (heat transfer)			
Nusselt	Nu	hl/λ	
Prandtl	Pr	ν/a	$a \equiv \lambda/(\rho C_p)$
Grashof	Gr	$\beta\Delta T g l^3/\nu^2$	$\equiv\beta\Delta T$Ga
Fourier	Fo	at/l^2	
Péclet	Pe	vl/a	$\equiv$Re Pr
Rayleigh	Ra	$\beta\Delta T g l^3/(a\nu)$	$\equiv$Gr Pr
Stanton	St	$h/(v\rho C_p)$	Nu/(Re Pr)
Thermal unit operations (mass transfer)			
Sherwood	Sh	kl/D	k—mass transfer coefficient
Schmidt	Sc	ν/D	
Bodenstein	Bo	vl/D_{ax}	D_{ax}—axial disp. coefficient
Lewis	Le	a/D	$\equiv$Sc/Pr
Stanton	St	k/v	$\equiv$Sh/(Re Sc)
Chemical reaction engineering			
Arrhenius	Arr	$E/(RT)$	E—activation energy
Hatta	Hat_1	$(k_1 D)^{1/2}/k_L$	First order reaction
	Hat_2	$(k_2 c_2 D)^{1/2}/k_L$	Second order reaction
Damköhler	Da	$\frac{cH_R}{C_p\rho T_0}$	Genuine (5)
	Da_I	$k_1\tau$	τ—residence time
	Da_{II}	$k_1 l^2/D$	$\equiv Da_I$ Bo
			$\equiv Da_I$ Re Sc
	Da_{III}	$k_1\tau\ (\frac{cH_R}{C_p\rho T_0})$	$\equiv Da_I\ (\frac{cH_R}{C_p\rho T_0})$
	Da_{IV}	$\frac{k_1 cH_R l^2}{\lambda T_0}$	$\equiv Da_I$ Re Pr $(\frac{cH_R}{c_p\rho T_0})$

2. *Reliable scale-up of the desired operating conditions from the model to the full-scale plant.* According to the theory of models, two processes may be considered similar to one another if they take place under geometrically similar conditions and all dimensionless numbers, which describe the process, have the same numerical value.
3. *A deeper insight into the physical nature of the process.* By presenting experimental data in a dimensionless form, one distinct physical state can be isolated from the other (e.g., turbulent or laminar flow region) and the effect of individual physical variables can be identified.
4. *Flexibility in the choice of parameters and their reliable extrapolation within the range covered by the dimensionless numbers.* These advantages become clear if one considers the well-known Reynolds number, $\mathrm{Re} = vL/\nu$, which can be varied by altering the characteristic velocity v, or a characteristic length L, or the kinematic viscosity ν. By choosing appropriate model fluids, the viscosity can be very easily altered by several orders of magnitude. Once the effect of the Reynolds number is known, extrapolation of both v and L are allowed within the examined range of Re.

Area of Applicability of Dimensional Analysis

The application of dimensional analysis is indeed heavily dependent on the available knowledge. The following five steps (Fig. 5) can be outlined as:

1. The physics of the basic phenomenon is unknown.
   → Dimensional analysis cannot be applied.
2. Enough is known about the physics of the basic phenomenon to compile a first, tentative relevance list.
   → The resultant pi set is unreliable.
3. All the relevant physical variables describing the problem are known.
   → The application of dimensional analysis is unproblematic.
4. The problem can be expressed in terms of a mathematical equation.
   → A closer insight into the pi relationship is feasible and may facilitate a reduction of the set of dimensionless numbers.
5. A mathematical solution of the problem exists.
   → The application of dimensional analysis is superfluous.

It must, of course, be said that approaching a problem from the point of view of dimensional analysis also remains useful even if all the variables relevant to the problem are not yet known: The timely application of dimensional analysis may often lead to the discovery of forgotten variables or the exclusion of artifacts.

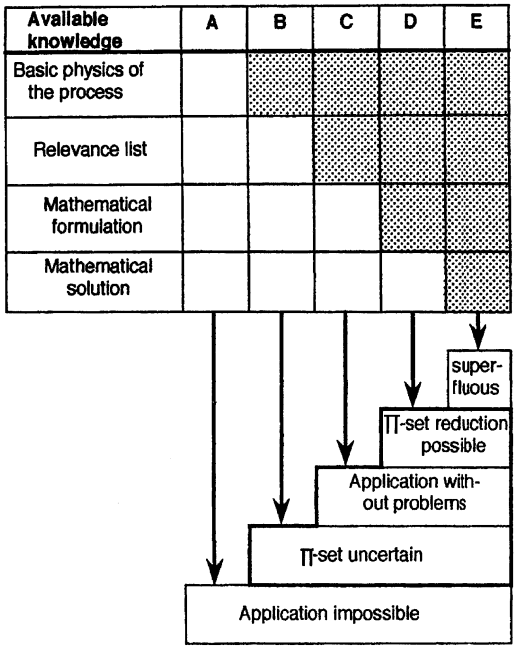

Figure 5 Graphical representation of the four levels of knowledge and their impact on the treatment of the problem by the dimensional analysis. *Source*: J. Pawlowski, personal communication, 1984.

Experimental Methods for Scale-Up

In the Introduction a number of questions were posed which are often asked in connection with model experiments.

How small can a model be? The size of a model depends on the scale factor L_T/L_M, and on the experimental precision of measurement. Where $L_T/L_M = 10$, a $\pm 10\%$ margin of error may already be excessive. A larger scale for the model will therefore have to be chosen to reduce the error.

Is one model scale sufficient or should tests be carried out in models of different sizes? One model scale is sufficient if the relevant numerical values of the dimensionless numbers necessary to describe the problem (the so-called "process point" in the pi space describing the operational condition of the technical plant) can be adjusted by choosing the appropriate process parameters or physical properties of the model material system. If this is not possible, the process characteristics must be determined in models of different sizes, or the process point must be extrapolated from experiments in technical plants of different sizes.

When must model experiments be carried out exclusively with the original material system? Where the material model system is unavailable

(e.g., in the case of non-Newtonian fluids) or where the relevant physical properties are unknown (e.g., foams, sludge, and slimes) the model experiments must be carried out with the original material system. In this case, measurements must be performed in models of various sizes (cf. Example 4).

Partial Similarity

The theory of models requires that in scale-up from a model (index $_M$) to industrial scale (index $_T$), not only must the geometric similarity be ensured but also all dimensionless numbers describing the problem must retain the same numerical values ($\Pi_i = \text{idem}$). This means that in scale-up of boats or ships, for example, the dimensionless numbers governing the hydrodynamics here

$$\text{Fr} \equiv \frac{v^2}{Lg} \quad \text{and} \quad \text{Re} \equiv \frac{vL}{\nu}$$

must retain their numerical values: $\text{Fr}_T = \text{Fr}_M$ and $\text{Re}_T = \text{Re}_M$.

It can easily be shown that this requirement cannot be fulfilled here.

Due to the fact that the gravitational acceleration g cannot be varied on Earth, the Froude number (Fr) of the model can be adjusted to that of the full-scale vessel only by its velocity v_M. Subsequently, $\text{Re} = \text{idem}$ can be achieved only by the adjustment of the viscosity of the model fluid. In cases where the model size is only 10% of the full size (scale factor $L_T/L_M = 10$), $\text{Fr} = \text{idem}$ is achieved in the model at $v_M = 0.32\ v_T$. To fulfill $\text{Re} = \text{idem}$, for the kinematic viscosity of the model fluid ν_M it follows:

$$\frac{\nu_M}{\nu_T} = \frac{v_M}{v_T} \times \frac{L_M}{L_T} = 0.32 \times 0.1 = 0.032$$

No liquid exists whose viscosity would be only 3% of that of water.

We have to realize that sometimes requirements concerning physical properties of model materials exist that cannot be implemented. In such cases only a partial similarity can be realized. For this, essentially only two procedures are available (for details see Refs. 5 and 10). One consists of a well-planned experimental strategy in which the process is divided into parts, which are then investigated separately under conditions of complete similarity. This approach was first applied by William Froude (1810–1879) in his efforts to scale-up the drag resistance of the ship's hull.

The second approach consists in deliberately abandoning certain similarity criteria and checking the effect on the entire process. This technique was used by Gerhard Damköhler (1908–1944) in his trials to treat a chemical reaction in a catalytic fixed bed reactor by means of dimensional analysis.

Here the problem of a simultaneous mass and heat transfer arises—they are two processes that obey completely different fundamental principles.

It is seldom realized that many "rules of thumb" utilized for scale-up of different types of equipment are represented by quantities, which fulfill only a partial similarity. As examples, only the volume-related mixing power P/V—widely used for scaling-up mixing vessels—and the superficial velocity v which is normally used for scale-up of bubble columns, should be mentioned here.

The volume-related mixing power P/V presents an adequate scale-up criterion only in liquid/liquid dispersion processes and can be deduced from the pertinent process characteristics $d_p/d \propto \mathrm{We}^{-0.6}$ (d_p—particle or droplet diameter; We—Weber number). In the most common mixing operation, the homogenization of miscible liquids, where a macromixing and back mixing is required, this criterion fails completely (10).

Similarly, the superficial velocity v or v_G of the gas throughput as an intensity quantity is a reliable scale-up criterion only in mass transfer in gas/liquid systems in bubble columns. In mixing operations in bubble columns, requiring the whole liquid content be back mixed (e.g., in homogenization), this criterion completely loses its validity (10).

We must draw the following conclusion: A particular scale-up criterion that is valid in a given type of apparatus for a particular process is not necessarily applicable to other processes occurring in the same device.

TREATMENT OF VARIABLE PHYSICAL PROPERTIES BY DIMENSIONAL ANALYSIS

It is generally assumed that the physical properties of the material system remain unaltered in the course of the process. Process equations, e.g., the heat characteristics of a mixing vessel or a smooth straight pipe

$$\mathrm{Nu} = f(\mathrm{Re}, \mathrm{Pr}) \tag{27}$$

are valid for any material system with Newtonian viscosity and for any constant process temperature, i.e., for any *constant* physical property.

However, constancy of physical properties cannot be assumed in every physical process. A temperature *field* may well generate a viscosity *field* or even a density *field* in the material system treated. In non-Newtonian (pseudoplastic or viscoelastic) liquids, a shear rate can also produce a viscosity *field*.

In carrying out a scale-up, the industrial process has to be similar to the laboratory process in every relation. Besides the geometric and process-related similarity, it is self-evident that also the fluid dynamics of the material system has to behave similarly. This requirement represents normally no problems when Newtonian fluids are treated. But it can cause problems, e.g., in some biotechnological processes—when material systems are involved which exhibit non-Newtonian viscosity behavior. Then the shear stress exerted by the stirrer causes a viscosity field.

Although most physical properties (e.g., viscosity, density, heat conductivity and capacity, and surface tension) must be regarded as variable, it is of particular value that viscosity can be varied by many orders of magnitude under certain process conditions (5,11). In the following, dimensional analysis will be applied exemplarily to describe the temperature dependency of the viscosity and the viscosity of non-Newtonian fluids (pseudoplastic and viscoelastic, respectively) as influenced by the shear stress.

Dimensionless Representation of the Material Function

Similar behavior of a certain physical property common to different material systems can *only* be visualized by dimensionless representation of the material function of that property (here the viscosity μ). It is furthermore desirable to formulate this function as uniformly as possible. This can be achieved by the "standard representation" (6,11) of the material function in which a standardized transformation of the material function $\mu(T)$ is defined in such a way that the expression produced meets the requirement

$$\mu/\mu_0 = \phi\{-\gamma_0(T - T_0)\} \tag{28}$$

and also meets the requirement

$$(0) = \phi'(0) = 1$$

where $\gamma_0 \equiv (\frac{1}{\mu}\frac{\delta\mu}{\delta T})$ T_0—temperature coefficient of the viscosity and $\mu_0 \equiv \mu(T_0)$. T_0 is *any* reference temperature.

Figure 6 shows the dependency $\mu(T)$ for eight different liquids with greatly different temperature coefficients of the viscosity, whose viscosities cover six decades within the range of $T = 20$–$80°C$. Figure 7 depicts the standard representation of this behavior. Surprisingly this proves that all these liquids behave similarly in the $\mu(T)$ respect. In addition, it proves that this standard representation is invariant to reference temperature. Water is a special juice; it behaves like the other liquids only in the vicinity of the standardization range $\gamma_0(T-T_0) \approx 0$.

What does Figure 7 imply? It implies that model measurements can be performed with any of these liquids in the temperature range given by the experiments and will provide accurate data for the industrial plant utilizing the others.

Pi Set for Temperature-dependent Physical Properties

The type of dimensionless representation of the material function affects the (extended) pi set within which the process relationship is formulated (for more information, see Ref. 11). When the standard representation is

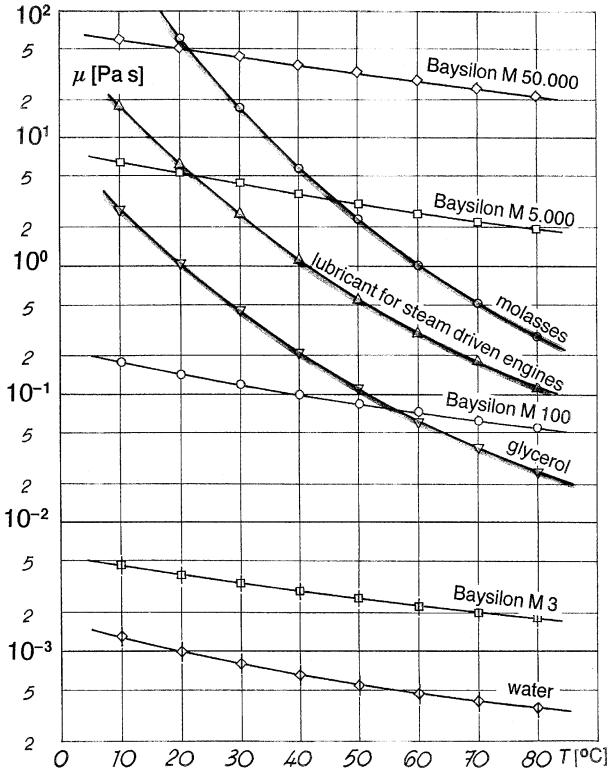

Figure 6 Temperature dependency of the viscosity, $\mu(T)$, for eight different liquids. (Baysilon is a silicone oil of the BAYER AG, Germany.)

used, the relevance list must include the reference viscosity μ_0 and the reference density ρ_0 instead of μ and ρ and incorporate three additional parameters, γ_0, β_0, T_0. This leads to three additional dimensionless numbers in the process characteristics. With regard to the heat transfer characteristics of a mixing vessel or a smooth straight pipe, Equation (27), it now follows that,

$$\mathrm{Nu} = f(\mathrm{Re}_0, \mathrm{Pr}_0, \gamma_0 \Delta T, \beta_0 \Delta T, \Delta T/T_0), \tag{29}$$

where the index $_0$ in Re and Pr denotes that these two dimensionless numbers are to be formed with μ_0 and ρ_0 (which are the reference numerical values of μ and ρ at T_0).

If we consider that the standard transformation of the material function can be expressed invariantly with regard to the reference temperature

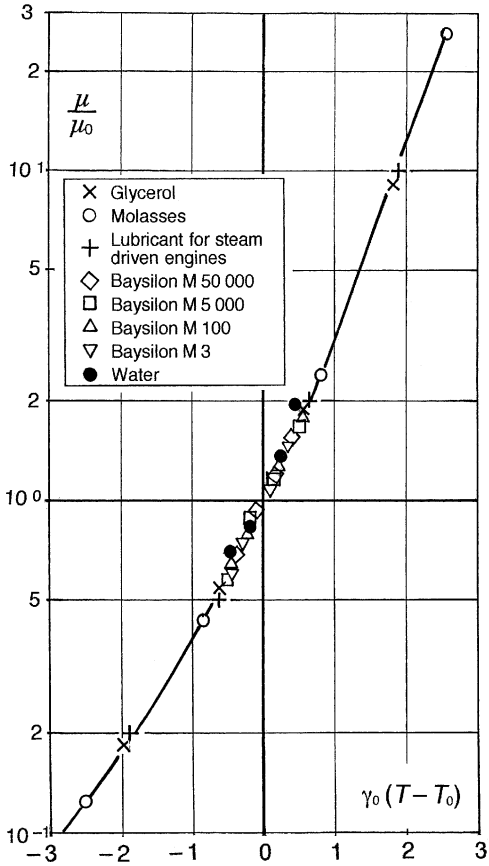

Figure 7 Standard representation of the dependency $\mu(T)$ for these liquids. The fitting curve presents the reference-invariant function χ after Pawlowski. The numerical value of the parameter μ of this function is -1.2 for water and -0.167 for other fluids. Logarithmic variation is 5.25×10^{-3} for water and 1.51×10^{-2} for other fluids. *Source*: From Ref. 11, Chapter 8.2.

T_0 (Fig.7), then the relevance list is extended by only two reference parameters, γ_0 and β_0. This, in turn, leads to only two additional dimensionless numbers. For the above problem, it now follows that

$$\mathrm{Nu} = f(\mathrm{Re}_0, \mathrm{Pr}_0, \gamma_0 \Delta T, \beta_0 \Delta T) \tag{30}$$

Non-Newtonian Liquids

The main characteristics of Newtonian liquids is that simple shear flow (e.g., Couette flow) generates shear stress τ, which is proportional to the shear rate

$\dot{\gamma} \equiv dv/dy$ (per sec). The proportionality constant, the dynamic viscosity μ, is the only material constant in Newton's law of friction:

$$\tau = \mu\dot{\gamma} \tag{31}$$

μ depends only on pressure and temperature.

In the case of non-Newtonian liquids, μ depends on $\dot{\gamma}$ as well. These liquids can be classified in various categories of materials depending on their flow behavior: $\mu(\dot{\gamma})$ —flow curve and $\mu(\tau)$ —viscosity curve.

Pseudoplastic Fluids

An extensive class of non-Newtonian fluids is formed by pseudoplastic fluids whose flow curves obey the so-called "power law"

$$\tau = K\dot{\gamma}^{m} \rightarrow \mu_{\text{eff}} = K\dot{\gamma}^{(m-1)} \tag{32}$$

These liquids are known as *Ostwald-de Waele* Fluids. Figure 8 depicts a typical course of such a flow curve.

Figure 9 shows a dimensionless standardized material function of two pseudoplastic fluids often used in biotechnology. It proves that the examined polymers (CMC—a chemical polymer and Xanthane—a biopolymer) are not completely similar to each other; if they were, the exponent m must not have been different by a factor of 2 (insert in Fig. 9).

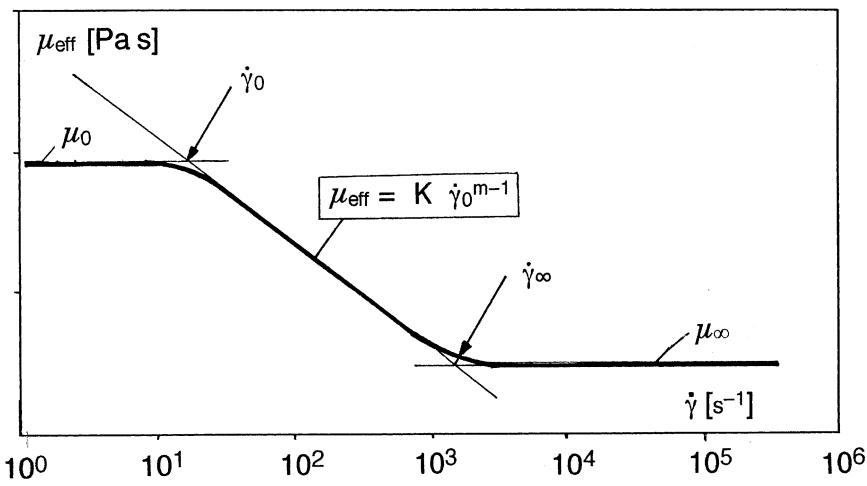

Figure 8 Typical course of the flow curve of an Ostwald-de Waele fluid obeying the so-called "power law" behavior.

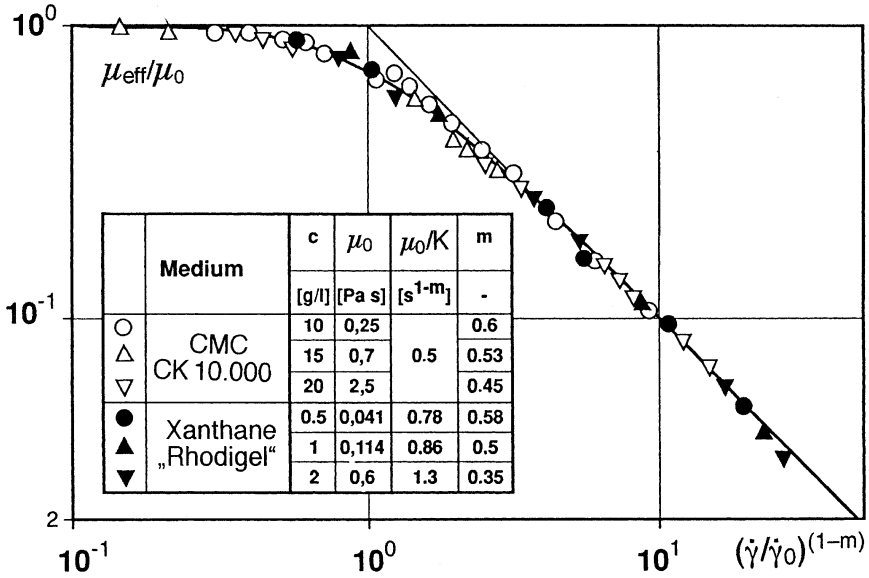

Figure 9 Dimensionless standardized material function of two pseudoplastic fluids [carboxymethyl-cellulose (CMC) and Xanthane] often used in biotechnology. *Source*: From Ref. 12.

Viscoelastic Liquids

Almost every biological solution of low viscosity [but also viscous biopolymers like xanthane and dilute solutions of long-chain polymers, e.g., carboxymethyl-cellulose (CMC), polyacrylamide (PAA), polyacrylnitrile (PAN), etc.] displays not only viscous but also viscoelastic flow behavior. These liquids are capable of storing a part of the deformation energy elastically and reversibly. They evade mechanical stress by contracting like rubber bands. This behavior causes a secondary flow that often runs contrary to the flow produced by mass forces (e.g., the liquid "climbs" the shaft of a stirrer, the so-called "Weissenberg effect").

Elastic behavior of liquids is characterized mainly by the ratio of first differences in normal stress, N_1, to the shear stress, τ. This ratio, the Weissenberg number $\mathrm{Wi} = N_1/\tau$, is usually represented as a function of the rate of shear $\dot{\gamma}$.

Another often used representation of the viscoelastic flow behavior utilizes normal stress coefficients $\Psi_i = N_i/\dot{\gamma}^2$. Figure 10 depicts flow curves of a family of PAA/water solutions differing in concentrations and therefore in their viscosities. Normalized by the zero-shear viscosity μ_0 and by a constant shear rate $\dot{\gamma}_0$ at a shear stress value of $\tau_0 = 1\ \mathrm{N/m^2}$ they produce master curves for viscosity and the normal stress coefficient. The preparation

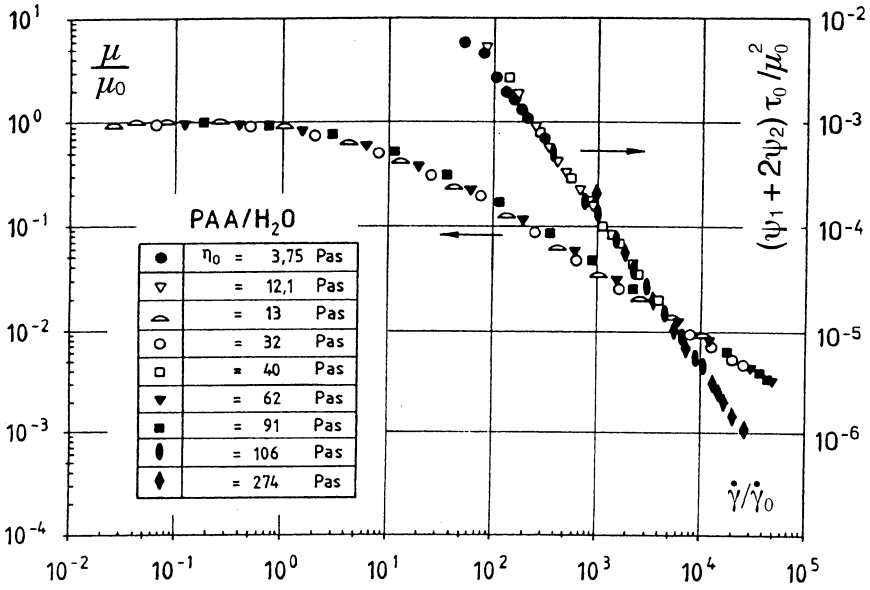

Figure 10 Flow curves of a family of polyacrylamide (PAA)/water-solutions of different concentrations and viscosities. Left side: normalized viscosity curves $\mu/\mu_0 = f_1(\dot{\gamma}/\dot{\gamma}_0)$, right side: normalized stress coefficients $(\Psi_1 + 2\Psi_2)\,\tau_0/{\mu_0}^2 = f_2$. *Source*: From Ref. 13.

of appropriate rheological substances as a set of liquids with similar rheological properties is indispensable if scale-up measurements have to be performed in differently scaled vessels. This will be demonstrated by the following example concerning the power consumption of a stirrer in a PAA/water solution.

PI SET AND THE POWER CHARACTERISTICS OF A STIRRER IN A VISCOELASTIC FLUID

In Example 5.1, the working out of the power characteristics of a stirrer in a Newtonian fluid is presented in detail. It is shown how a relevance list containing five parameters: stirrer power P, stirrer diameter d, density ρ, and viscosity μ of the liquid and the stirrer speed n

$$\{P, d, \rho, \mu, n\}$$

is condensed to only two dimensionless numbers

$$\Pi_1 \equiv \frac{P}{\rho n^3 d^5} \equiv \text{Ne} \quad \text{(Newton number)}$$

$$\Pi_2 \equiv \frac{nd^2\rho}{\mu} \equiv \mathrm{Re} \quad \text{(Reynolds number)}$$

and therefore the process characteristics are given by the dependency

$$\mathrm{Ne} = f(\mathrm{Re}) \tag{33}$$

In a viscoelastic liquid, the relevance list must be extended by two rheological parameters known in advance: shear rate $\dot{\gamma}_0$ and the first difference in normal stress $N_{1,0}$. Besides this, the viscosity μ must be replaced by the zero viscosity $\mu_{0,}$ which is also known in advance (Fig. 8). The relevance list reads:

$$\{P,\ d, \rho,\ \mu_0,\ N_{1,0},\ \dot{\gamma}_0,\ n\}$$

resulting in $7 - 3 = 4$ dimensionless numbers,

$$\frac{P}{\rho n^3 d^5} \equiv \mathrm{Ne}, \quad \frac{nd^2\rho}{\mu_0} \equiv \mathrm{Re}_0, \quad \frac{N_{1,0}}{\mu_0\dot{\gamma}_0} \equiv \frac{N_{1,0}}{\tau_0} \equiv \mathrm{Wi}, \quad \frac{\dot{\gamma}_0}{n} \tag{34}$$

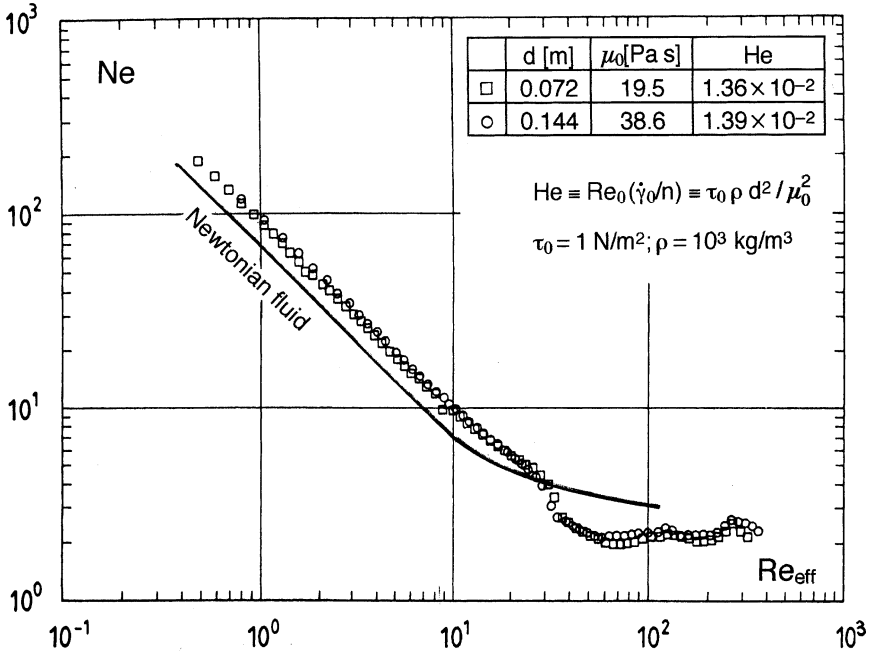

Figure 11 Power characteristics of a Rushton turbine stirrer under given geometric conditions, measured in two differently scaled vessels (scale 1:2) and fitting the flow behavior of the viscoelastic fluid [polyacrylamide (PAA) solution] by changing its viscosity. *Source*: From Ref. 13.

Three dimensionless numbers contain the stirrer speed n. By combining two of them, we obtain a new number that is known as the Hedström number,

$$\mathrm{He} \equiv \mathrm{Re}_0 \frac{\dot{\gamma}_0}{n} \equiv \frac{d^2 \rho\ \dot{\gamma}_0}{\mu_0} \equiv \frac{d^2 \rho\ \tau_0}{\mu_0^2}$$

We immediately discover that in scaling-up or -down, the quotient d/μ_0 has to remain constant: halving d requires halving μ_0. Therefore, in model measurements with non-Newtonian liquids, a family of liquids with similar rheological behavior (Fig. 10) is required.

By keeping the Weissenberg number Wi (a pure material number) and the Hedström number He constant, measurements are performed and presented in a dimensionless frame:

$$\mathrm{Ne} = f(\mathrm{Re}_0) \quad \text{at Wi, He} = \text{const.} \tag{35}$$

Figure 11 depicts the power characteristics of a Rushton turbine stirrer in geometrically similar cylindrical vessels ($H/\mathrm{D} = 1$; $\mathrm{D}/d = 2$) without baffles. To keep the Hedström number constant at different scales, viscosity of the PAA solutions had to be fitted as discussed above.

APPLICATION OF SCALE-UP METHODS IN PHARMACEUTICAL ENGINEERING

Optimum Conditions for the Homogenization of Liquid Mixtures

The homogenization of miscible liquids is one of most frequent mixing operations. It can be executed properly if the power characteristics and the mixing time characteristics of the stirrer in question are known. If these characteristics are known for a series of common stirrer types under favorable installation conditions, optimum operating conditions can be found by evaluating which type of stirrer operates within the requested mixing time θ with the lowest power consumption P and hence the minimum mixing work ($P\theta = \min$) in a given material system and a given vessel (vessel diameter D).

Example 5.1: Power Characteristics of a Stirrer

The relevance list of this task consists of the target quantity (mixing power P) and the following parameters: stirrer diameter d, density ρ, kinematic viscosity ν of the liquid, and stirrer speed n:

$$\{P; d; \rho; \nu; n\} \tag{36}$$

By choosing the dimensional matrix

	ρ	d	n	P	ν
Mass (M)	1	0	0	1	0
Length (L)	−3	1	0	2	2
Time (T)	0	0	−1	−3	−1
		Core matrix		Residual matrix	

only one linear transformation is necessary to obtain the unity matrix:

	ρ	d	n	P	ν
M	**1**	0	0	1	0
3M + L	0	**1**	0	5	2
−T	0	0	**1**	3	1
		Unity matrix		Residual matrix	

The residual matrix consists of only two parameters, therefore only two pi numbers result:

$$\Pi_1 \equiv \frac{P}{\rho^1 n^3 d^5} = \frac{P}{\rho n^3 d^5} \equiv \text{Ne (Newton number)}$$

$$\Pi_2 \equiv \frac{\nu}{\rho^0 n^1 d^2} = \frac{\nu}{n d^2} \equiv \text{Re}^{-1} \text{ (Reynolds number).}$$

The process characteristics

$$\text{Ne} = f(\text{Re}) \tag{37}$$

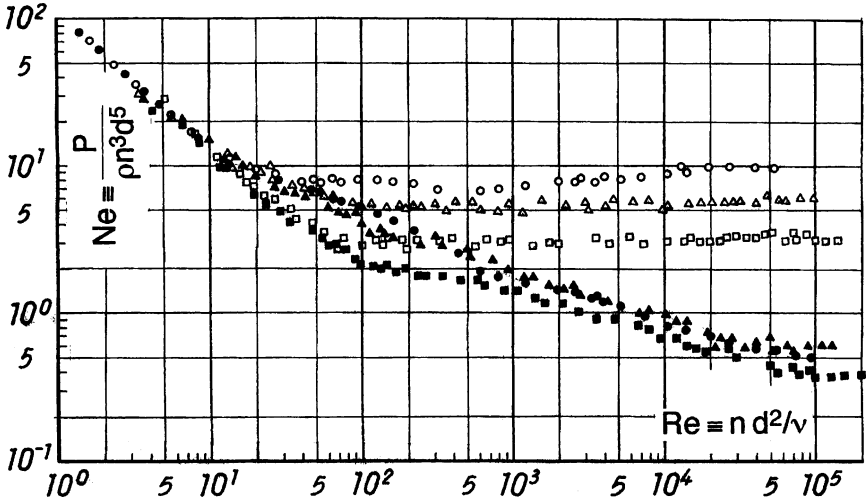

Figure 12 Power characteristics of three slowly rotating stirrers (leaf, frame, cross-beam stirrer) installed in a vessel with and without baffles. *Source*: From Ref. 14.

for three well-known slowly rotating stirrers (leaf, frame, and cross beam stirrer) are presented in Figure 12.

Stirrer geometry and the installation conditions are given in Figure 13. From Figure 12, we learn the following:

1. In the range $\mathrm{Re} < 20$, the proportionality $\mathrm{Ne} \propto \mathrm{Re}^{-1}$ is found, thus resulting in the expression $\mathrm{Ne}\,\mathrm{Re} \equiv P/(\eta n^2 d^3) = \text{const}$. Density is irrelevant here because we are dealing with the creeping flow region.
2. In the range $\mathrm{Re} > 50$ (vessel with baffles) or $\mathrm{Re} > 5 \times 10^4$ (unbaffled vessel), because the Newton number $\mathrm{Ne} \equiv P/(\rho n^3 d^5)$ remains constant. In this case, viscosity is irrelevant we are dealing with a turbulent flow region.
3. Understandably, the baffles do not influence the power characteristics within the creeping flow region where viscosity forces prevent rotation of the liquid. However, their influence is extremely strong at $\mathrm{Re} > 5 \times 10^4$. Here, the installation of baffles under otherwise unchanged operating conditions increases the power consumption of the stirrer by a factor of 20.
4. The power characteristics of these three stirrers do not differ much from each other. This is understandable because their mixing patterns are very similar.

Example 5.2: Mixing Time Characteristics of a Stirrer

Mixing time θ is the time necessary to completely homogenize an admixture with the liquid contents of the vessel. It can easily be determined visually by a decolorization reaction (neutralization, redox reaction in the presence of a color indicator). The relevance list of this task consists of the target quantity (mixing time θ) and of the same parameters as in the case of mixing power—on condition that (contrary to Example 3) both liquids have similar physical properties:

$$\{\theta; d; \rho; \nu; n\} \tag{38}$$

This relevance list yields in the two parametric mixing time characteristics

$$n\theta = f(\mathrm{Re}) \tag{39}$$

For the three stirrer types treated in this example, the mixing time characteristics are presented in Figure 13.

One should not be confused by the course of the $n\theta$ (Re) curves: the mixing time does not increase with higher Re numbers, but simply

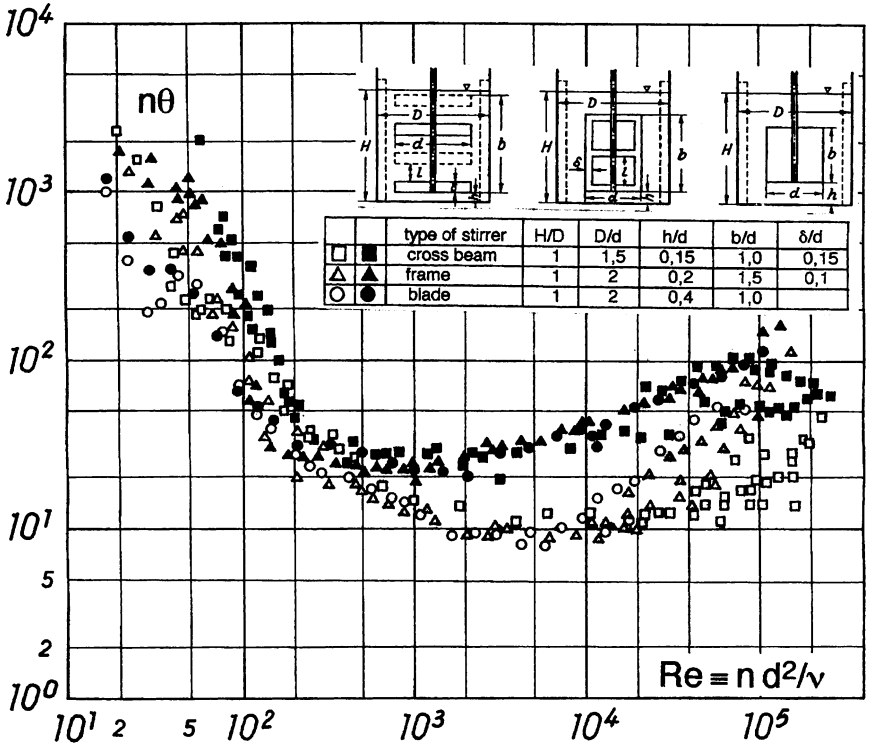

Figure 13 Mixing time characteristics of three slowly rotating stirrers (leaf, frame, crossbeam stirrer) in a vessel with and without baffles. To correlate the data in order to emphasize the similarity, $n\theta$ values of the crossbeam stirrer were multiplied by 0.7 and of the leaf stirrer by 1.25. *Source*: From Ref. 14.

diminishes more slowly, until at $\mathrm{Re} \approx 10^6$ the minimum achievable mixing time is reached:

$$n\theta \propto \mathrm{Re} \rightarrow \theta \propto \frac{d^2}{\nu} \quad (\mathrm{Re} \geq 10^6) \tag{40}$$

From Equation (38), we learn that the minimum achievable mixing time corresponds to the square of the stirrer diameter: bigger volumes require longer mixing times.

Example 5.3: Minimum Mixing Work ($P\theta = \min$) for Homogenization

To gain information on minimum mixing work ($P\theta = \min$) necessary for homogenization, the mixing time characteristics, as well as the power

characteristics, have to be combined in a suitable manner. Both of them contain the rotational speed n and the stirrer diameter d, the knowledge of which would unnecessarily constrict the statement. Therefore, the ratio D/d, tank diameter/stirrer diameter, which is known for the often used stirrer types, must also be incorporated.

From the pi frame

$$\{\mathrm{Ne}, n\theta, \mathrm{Re}, D/d\} \tag{41}$$

the following two dimensionless numbers can now be formed:

$$\Pi_1 = \mathrm{Ne}\ \mathrm{Re}\ D/d = \frac{PD}{\rho\nu^3} = \frac{PD\rho^2}{\eta^3} \tag{42}$$

$$\Pi_2 = n\theta \mathrm{Re}^{-1}(D/d)^2 = \frac{\theta\nu}{D^2} = \frac{\theta\eta}{D^2\rho} \tag{43}$$

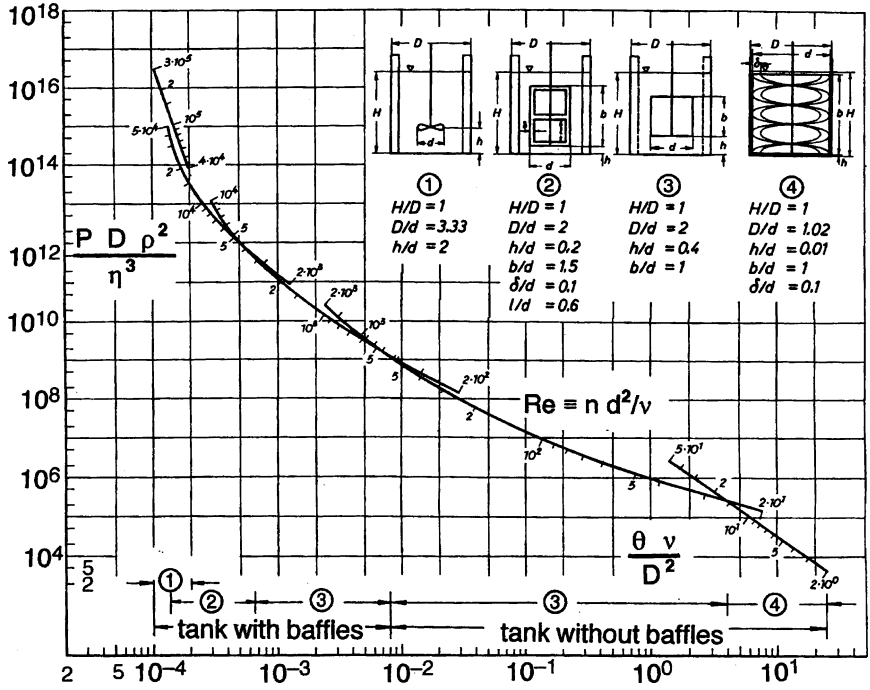
P D ρ²
η³
Re ≡ n d²/ν
θ ν
D²
① H/D = 1 D/d = 3.33 h/d = 2
② H/D = 1 D/d = 2 h/d = 0.2 b/d = 1.5 δ/d = 0.1 l/d = 0.6
③ H/D = 1 D/d = 2 h/d = 0.4 b/d = 1
④ H/D = 1 D/d = 1.02 h/d = 0.01 b/d = 1 δ/d = 0.1
tank with baffles
tank without baffles

Figure 14 Work sheet for the determination of optimum working conditions for the homogenization of liquid mixtures in mixing vessels. *Source*: From Ref. 14.

Figure 14 shows this relationship $\Pi_1 = f(\Pi_2)$ for those stirrer types which exhibit the lowest Π_1 values within a specific range of Π_2, i.e., the stirrers requiring the least power in this range. It represents a work sheet for the determination of optimum working conditions for the homogenization of liquid mixtures in mixing vessels.

This graph is extremely easy to use. The physical properties of the material system, the diameter of the vessel (D), and the desired mixing time (θ) are all known and this is enough to generate the dimensionless number Π_2.

a. From the numerical value of Π_2 the stirrer type and baffling conditions can be read off the abscissa. The diameter of the stirrer and the installation conditions can be determined from data on stirrer geometry in the sketch. The curve $\Pi_1 = f(\Pi_2)$ in Figure 14 then provides information as the numerical values of Π, and Re.
b. The numerical value of Π_1 can be read at the intersection of the Π_2 value with the curve. Power consumption P can then be calculated.
c. The numerical value of Re can be read from the Re scale at the same intersection. This, in turn, makes it possible to determine the rotational speed of the stirrer.

For further examples of this optimization technique, see References 5 and 11.

Example 6: Scale-Up of Mixers for Mixing of Solids

In the final state, the mixing of solids (e.g., powders) can only lead to a stochastically homogeneous mixture. We can therefore use the theory of random processes to describe this mixing operation. In the present example from Reference 15, we will concentrate on a mixing device in which the position of the particles is adequately given by the x coordinate. Furthermore, we will assume that the mixing operation can be described as a stochastic process without "after-effects." This means that only the actual condition is important and not its history. The temporal course of this so-called Markov process can be described with the second Kolmogorov equation. In the case of a mixing process without selective convectional flows (requirement: $\Delta\rho \approx 0$ and $\Delta d_p \approx 0$; see Ref. 16), the solution of Fick's diffusion equation gives a cosine function for the local concentration distribution, the amplitude of which decreases exponentially with the dimensionless time $\theta D_{eff}/(\pi^2 L^2)$ (Fig. 15). (The variation coefficient, v, is defined as the standard deviation σ divided by the arithmetic mean $\bar{x}$: $v \equiv \sqrt{\sigma^2}/\bar{x}$.)

Let us now consider this process using dimensional analysis. For a plow mixer (see sketch in Figure 15) we have the following parameters:

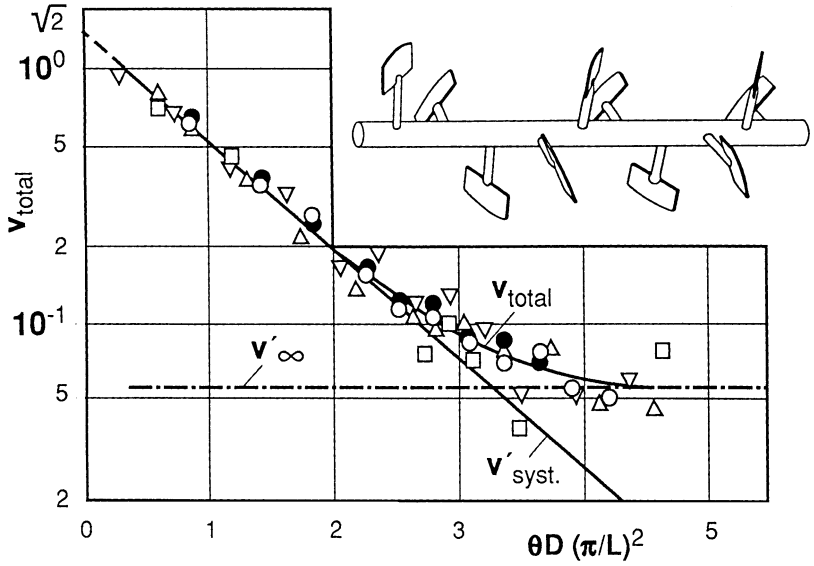

Figure 15 Variation coefficient v as a function of the dimensionless mixing time for different L/D ratios. Copper and nickel particles of $d_\mathrm{p} = 300$–$400\,\mu\mathrm{m}$, fill degree of the drum $\phi = 35\%$, Froude number of the paddle shaft $\mathrm{Fr} = 0.019$. *Source*: From Ref. 15.

Target quantity	
v	Variation coefficient as a measure for quality of mixture
Geometric parameters	
D, L	Diameter and length of the drum
d	Diameter of the paddle shaft
d_p	Mean particle diameter
ϕ	Degree of fill of the drum
Material properties	
D_eff	Effective axial dispersion coefficient
ρ	Density of the particles
Process parameters	
n	Rotational speed of the mixer
θ	Mixing time
$g\rho$	Solid gravity

The relevance list contains 11 parameters:

$$\{v; \mathrm{D}; L; d; d_\mathrm{p}; \phi; D_\mathrm{eff}; \rho; n; \theta; g\rho\} \tag{44}$$

After the exclusion of the dimensionless quantities v and ϕ and the obvious geometric pi numbers L/D, d/D, and d_p/D, the remaining three pi numbers are obtained via dimensional matrix:

$\theta\ n$	Mixing time number.
$D_{eff}/D^2 n \equiv Bo^{-1}$	Bo—Bodenstein number.
$g\rho/(\rho\ D\ n^2) \equiv Fr^{-1}$	Fr—Froude number.

The complete pi set contains eight pi numbers and reads:

$$\{v, L/D, d/D, d_p/D, \phi, \theta_n, Bo, Fr\} \tag{45}$$

To keep the rotational speed of the drum only in the process number Fr, we combine the other two accordingly with Fr and obtain:

$\theta D_{eff}/D^2$ and $gD^3/D_{eff}{}^2$.

The experimental results presented in Figure 15 were obtained in one single model ($D = 0.19$ m) with different lengths ($L/D = 1$; 1.5; 2; 2.5). The geometric and material numbers d/D, d_p/D, ϕ, and $gD^3/D_{eff}{}^2$ remained unchanged, as did Fr, because of the constant rotational speed of the paddle shaft $n = 50$/min. As a result, the measurements can be depicted only in the pi-space

$$\{v, \theta D_{eff}/D^2, L/D\} \tag{46}$$

whereby d/D, d_p/D, ϕ, $gD^3/D_{eff}{}^2$, Fr = idem. The result of these measurements is

$$v = f(\theta D_{eff}/L^2). \tag{47}$$

In other words, the mixing time (at Fr = const) required to attain a certain mixing quality increases with the square of the drum length L. In order to reduce the mixing time, the component to be mixed would have to be added in the middle of the drum or simultaneously at several positions.

Figure 15 shows experimental results in a single logarithmic graph. They are compared with the theoretical predictions of a stochastic Markov process. For details see Reference 15.

Entrop (17) reported the process characteristics of the Nauta® mixer. The Nauta® mixer utilizes the orbiting action of a helical screw, rotating on its own axis, to carry material upward, while revolving about the centerline of the cone-shaped housing near the wall for top-to-bottom circulation, (see the sketch in Fig. 16). Nauta® mixers of different sizes are not built geometrically similar to each other, but the diameter of the helical screw and its pitch are kept equal.

Mixing time characteristic of the Nauta® cone and screw mixer

Relevance list: In case of a pure convective mixing and $\Delta\rho$, $\Delta d_p \approx 0$, the particle size d_p is of no influence.

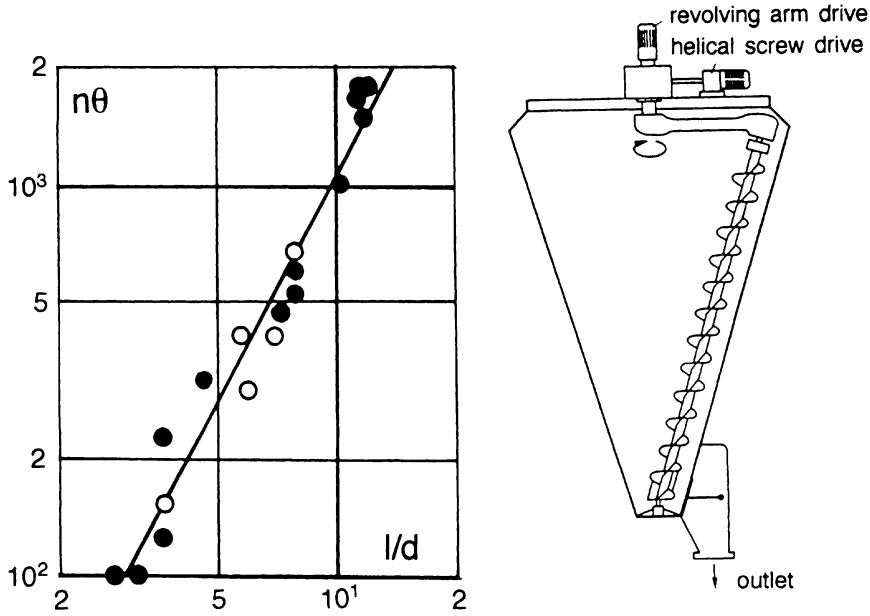

Figure 16 Mixing time characteristic of the Nauta® mixer and its drawing. *Source*: From Ref. 17.

Target quantity	
θ	Mixing time
Geometric parameters	
d, l	Diameter and length of the helical screw
Material property	
ρ	Density of the particles
Process parameters	
n, n_b	Rotational speed of the helical screw and of its beam
$g\rho$	Solid gravity

From the set of

$$\{\theta; d; l; \rho; n; n_b; g\rho\} \tag{48}$$

$7 - 3 = 4$ numbers will be produced. The pi-set reads:

$$\{n\theta, l/d, n_b/n, Fr \equiv n^2 d\rho/g\rho \equiv n^2 d/g\} \tag{49}$$

The measurements were executed under the the following conditions: mixer volume $V = 0.05$–$10\,\mathrm{m}^3$; diameter of the helical screw $d = 0.15$–$0.63\,\mathrm{m}$;

rotational speed of the helical screw $n = 30\text{–}120/\text{min}^{-1}$; $n_b/n = 20\text{–}70$; $\text{Fr} = 0.24\text{–}4$. Material systems were sand and fine-grained limestone.

The mixing time characteristic of the Nauta® mixer is given in Figure 16. It can be shown that the type of material has a negligible influence (proof that the density ρ is irrelevant indeed). Likewise, the number n_b/n has no effect within the used range. In contrast, the influence of the parameter l/d is very pronounced. The process equation reads:

$$n\theta = 13(l/d)^{1.93} \quad n_b/n = 20-70 \quad \text{Fr} = 0.24-4 \tag{50}$$

This means, in practice, that the mixing time is lengthened by the square of the length [compare to Eq. (45)].

The power characteristic of the Nauta® mixer has been found as follows

$$\text{Ne Fr} \equiv \frac{P}{nd^4 g\rho} \propto (l/d)^{1.62} \tag{51}$$

The expression for the mixing work, necessary for a given mixing quality, can be obtained by multiplying both process characteristics (48) and (49):

$$W = P\theta \propto d^{0.45} l^{3.55} \rho g \tag{52}$$

From the enery point of view, it is therefore advantageous to construct mixers of low heights and to provide them with helical screws of large diameters.

Example 7: Scale-Up of Single Screw Extruders for Mixing Highly Viscous Media

Single screw extruders are important mixing devices for highly viscous media. The mixing action results from the cross-channel flow (''leak flow'') in the full flights of the extruder caused by the combined actions of drag and pressure flow. The pressure flow can be greatly enhanced and varied by combining a single screw extruder with a gear-type rotary pump.

The pressure characteristics of such an extruder/pump combination is given by

$$Y \equiv \text{Eu Re } d/L \equiv \frac{\Delta p d}{\mu n L} = f_1(Q) \tag{53}$$

where Q represents the flow rate number $Q \equiv q/(nd^3)$; q—volumetric throughput: n—rotational speed: d, L—diameter and length of the screw housing. In the creeping flow ($\text{Re} < 100$) of Newtonian liquids, this is a linear dependency described by the analytical expression:

$$\frac{1}{y_1} Y + \frac{1}{q_1} Q = 1 \tag{54}$$

where y_1 and q_1 are the respective axis intercepts (Fig. 17).

In this representation, the throughput number Q is standardized by the intercept A_1. It is the numerical value of Q where the screw machine is conveying without pressure formation. With this kinematic flow parameter, $\Lambda \equiv Q/A_1$, the state of flow of a screw machine can be outlined more distinctly.

From the three ranges of the conveying characteristics, only the middle one, $0 < \Lambda < 1$ (the so-called "active conveying range" of the screw machine), can be implemented by suitable throttling and/or a change in the rotational speed alone, without an additional conveying device. At $\Lambda = 0$, the screw machine is fully choked and the highest pressure builds up. At $\Lambda = 1$, the highest throughput is achieved without a pressure build-up.

In the other two ranges, the gear-type rotary pump has to enter into action. If the pump pushes the liquid in the same direction as the screw, the range $\Lambda > 1$ results. The conveying action of the screw machine is "run over" by the conveying action of the pump. In this operation, an excellent heat transfer between the housing and the liquid can be obtained (18).

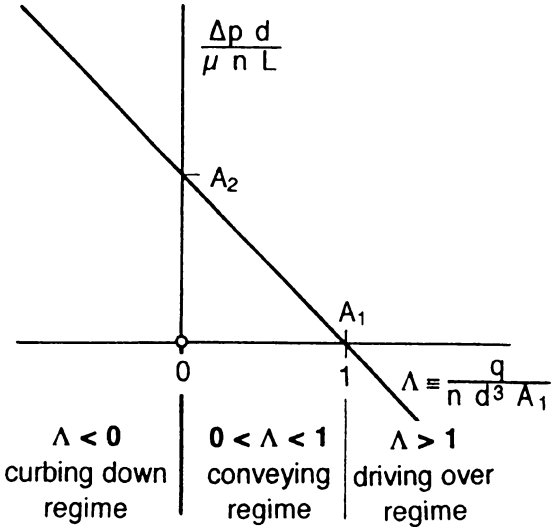

Figure 17 Subdivision of the typical working ranges of an extruder/pump combination by the kinematic flow parameter $\Lambda \equiv Q/A_1$.

At $\Lambda < 0$, the pump pushes the liquid against the conveying sense of the screw. In this flow range, the screw machine is an excellent mixing device.

Figure 18 depicts the mixing characteristics of the extruder/pump combination and confirms the above statement. At $\Lambda = 0$, the liquid throughput is zero and the residence time unlimited. Here, the stochastic homogeneity is surely reached and the corresponding v value is $v \approx 0$. The fitting line in the range $0 < \Lambda < 1$ corresponds to the analytical expression $v = 0.52\ \Lambda^{1.79}$. Monograph (18) contains a series of suggestions concerning the scale-up of a combination single screw extruder/gear-type rotary pump for homogenization as well as for heat transfer.

Example 8: Scale-Up of Liquid Atomization (Liquid-in-Gas-Dispersion)

Liquid atomization is an important unit operation that is employed in a variety of processes. They include fuel atomization, spray drying, metal powder production, coating of surfaces by spraying, etc.

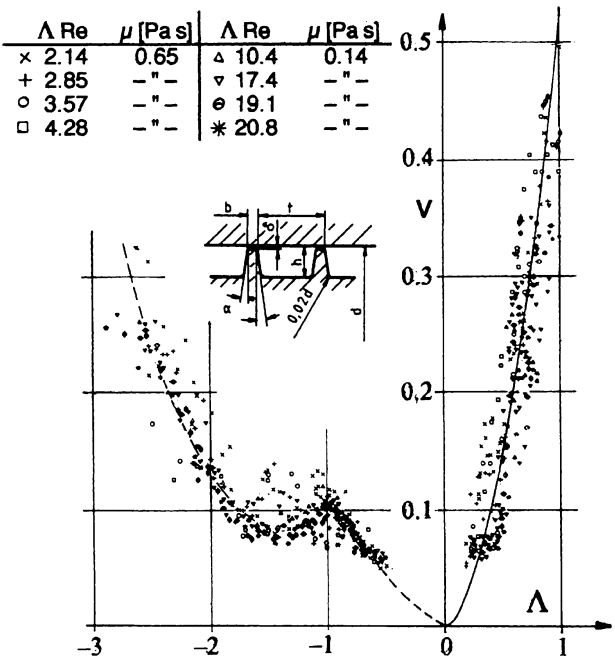

Figure 18 Homogenization effect of the extruder/pump combination. Influence of the kinematic flow parameter Λ on the variation coefficient v at the distribution of iron powder in silicone oil. $d = 60$ mm; $L/d = 5.23$. *Source*: Ref. 18, Figure 1.4.1.

In all these tasks, the achievable (as narrow as possible) droplet size distribution represents the most important target quantity. It is often described merely by the mean droplet size, the so-called "Sauter mean diameter" d_{32} (Ref. 19), which is defined as the sum of all droplet volumes divided by their surfaces. Mechanisms of droplet formation are:

1. The liquid jet formed by a pressure nozzle is inherently unstable. The breakup of the laminar jet occurs by symmetrical oscillation, sinusoidal oscillation, and atomization.
2. Liquid sheet formation by an appropriate nozzle is followed by rim disintegration, aerodynamic wave disintegration, and turbulent breakup.
3. Liquid atomization by a gas stream.
4. Liquid atomization by centrifugal acceleration.

Dimensionless process equations exist for all of these operations, (see Ref. 20) some of them will be represented in the following paragraphs.

As discharge velocity at the nozzle outlet increases, the following states appear in succession: dripping, laminar jet breakup, wave disintegration, and atomization. These states of flow are described in a pi space {Re, Fr, We_p}, whereby $We_p \equiv \rho v^2 d_p/\sigma$ represents the Weber number formed by the droplet diameter, d_p. To eliminate the flow velocity, v, these numbers are combined to give

$$Bd_p \equiv \frac{We}{Fr} \equiv \frac{\rho g d_p^2}{\sigma} \quad \text{(Bond number)} \tag{55}$$

and

$$Oh_p \equiv \frac{We^{1/2}}{Re} \equiv \frac{\mu}{(\sigma \rho d_p)^{1/2}} \quad \text{(Ohnesorge number)} \tag{56}$$

The subscript p indicates that these pi numbers are formed with the droplet diameter.

For a liquid dripping from a tiny capillary with diameter d, it follows:

$$\frac{d_p}{d} = 1.6\left(\frac{\rho g d^2}{\sigma}\right)^{-1/3} = 1.6\,Bd^{-1/3} \tag{57}$$

Broader tubes ($Bd > 25$) exert no influence of d. Then we obtain:

$$Bd_p \equiv \rho g d_p^2/\sigma = 2.9\text{–}3.3 \tag{58}$$

On the jet surface, waves are formed which grow rapidly at wave lengths of $\lambda > \pi d_j$ (d_j—jet diameter). The fastest wave disturbance takes place at the optimum wave length of

$$\lambda_{opt}/\pi d_j = \sqrt{2 + 6\,Oh}. \tag{59}$$

For a low-liquid viscosity, $d/d_j \approx 1.9$ applies. If liquid output pulsates, uniformly spaced droplets are obtained; here, $d/d_j \approx 1$.

With higher discharge velocities, laminar jets are produced that disintegrate to droplets at a certain distance from the capillary. The transition from dripping to liquid jet disintegration occurs at higher Weber numbers:

$$We \equiv \rho v^2 d/\sigma = 8 - 10. \tag{60}$$

At We < 8, gravitational acceleration also must be considered; thereby, the Bond number must be included in the process equation.

The working principle of hollow cone nozzles is that the liquid throughput is subjected to rotation by a tangential inlet and is then further accelerated in the conical housing toward the orifice (see the sketch in Figure 19). A liquid film with a thickness δ is thereby produced, which spreads to a hollow cone sheet and disintegrates into droplets at the discharge from the orifice.

At low-discharge velocities and low film thicknesses, the sheet disintegration is due to the oscillations caused by air motion. In this case, the film thickness has a large impact on the droplet size. In contrast, it is insignificant whether a pure liquid or a lime-water suspension (mass portion $\phi = 16$–64%) is treated (21).

By exceeding a certain discharge velocity, turbulence forces increase to such an extent that film disruption takes place immediately at the orifice. Now the droplet size is independent of the film thickness. This state of atomization is described by the critical Weber number. Measuring data obtained with hollow cone nozzles of different geometry and pure liquids as well as lime-water suspensions are represented in Figure 19. $We_{p,crit}$

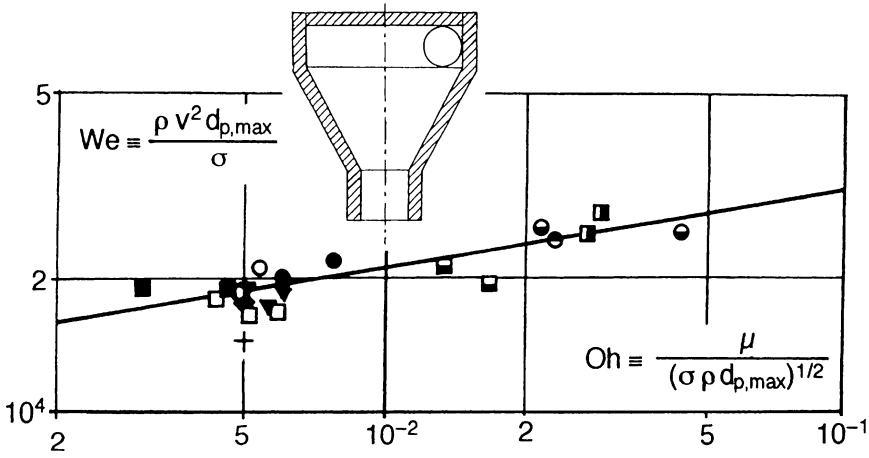

Figure 19 Liquid film atomization with hollow cone nozzles by turbulent forces. *Source*: From Ref. 21.

and the Ohnesorge number are formed by the largest stable droplet diameter, $d_{p,max}$. The pi equation reads:

$$We_{p,crit} = 4.5 \times 10^4 \ Oh_p^{1/6}$$

This equation (Ref. 21), is useless for scaling-up purposes because the (unknown) target quantity $d_{p,max}$ also appears in the process number Oh. In the combination

$$We_{p,crit} Oh_p^2 \equiv We/Re \equiv v\mu/\sigma \tag{61}$$

a new pi-number is obtained which does not contain $d_{p,max}$:

$$We_{p,crit} \equiv \rho v^2 d_{p,crit}/\sigma = 1.97 \times 10^4 (v\mu/\sigma)^{0.154} \tag{62}$$

This process equation can now serve for scaling-up $d_{p,max}$

Example 9: Standard Representation of Particle Strength of Various Solids as Function of Particle Size

Particle strength σ of solids plays an important role in the comminuting technology (crushing, grinding). It strongly depends on the particle diameter. At particle sizes below several millimeters, the strength to fracturing increases sharply because as the particle size decreases, material flaws become smaller and the particles more homogeneous.

Figure 20 depicts the dependence of particle strength σ on particle size d_p for a variety of solids (22). The differences in $\sigma(d_p)$ are so distinct that a similarity in strength of these materials cannot be anticipated. Whether or not laboratory measurements may be conducted with limestone and the results used to design a crusher or a grinder for quartz is a question that cannot be answered.

To examine the similarity in particle strength of these materials, a standard representation of this physical property must be calculated. Figure 21 shows it in the pi space

$$\sigma/\sigma_0 = \phi\{-\phi(d_p - d_{p,0})\} \tag{63}$$

in which the particle strength coefficient ϕ has been gained in a similar way as before the temperature coefficient of viscosity, γ_0 (Figure 7):

$$\phi \equiv \left(\frac{1}{\sigma_0}\frac{\partial\sigma}{\partial d_p}\right)_{d_{p,0}} \tag{64}$$

The curves in Figure 21 represent the so-called reference-invariant approximation (11) of individual point collectives. The bold curve, obtained

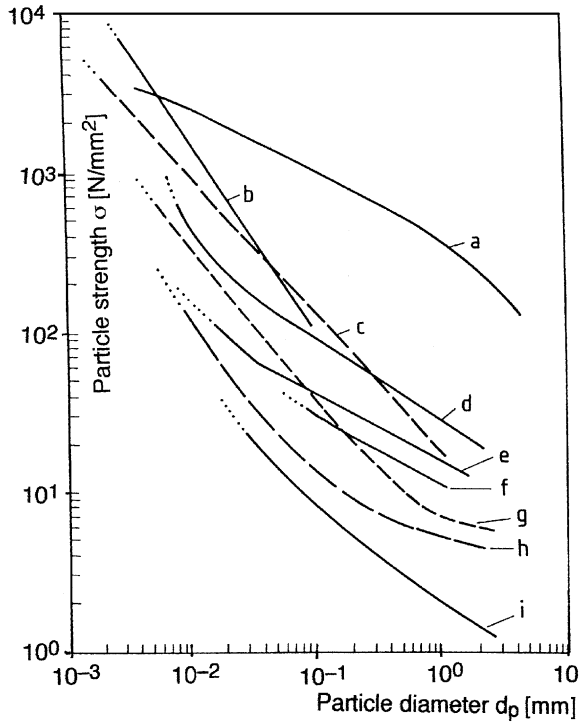

Figure 20 Particle strength σ of various solids as a function of particle size d_p. a, Glass beads; b, boron carbide; c, crystaline boron; d, cement clinker; e, marble; f, cane sugar; g, quartz; h, limestone; i, coal. *Source*: From Ref. 22.

with $\mu = -1.72$, describes the majority of the investigated material with a relative variation of 3.13×10^{-2}. These solids are similar to each other in this respect. The thin curves are for quartz ($\mu = -1.19$) and for boron carbide ($\mu = -0.80$). They deviate more than the others in the range of $\sigma/\sigma_0 < 1$.

The third dimensionless number, $\phi d_{p,0}$, resulting from the five parametric relevance list

$$\{\sigma, \sigma_0, d_p, d_{p,0}, \phi\} \tag{65}$$

is obviously irrelevant. These data could be described by a reference invariant approximation.

Example 10: Emulsification of Non-Miscible Liquids

Liquid/liquid emulsions consist of two or more non-miscible liquids. Classic examples of oil-in-water (O/W) emulsions are/milk, mayonnaise, lotions,

creams, water-soluble paints, and photo emulsions. As appliances serve dispersion and colloid mills, as well as high-pressure homogenizers. All of them utilize high-energy input to produce the finest droplets of the dispersion (mostly oil) phase. The aim of this operation is to produce the narrowest possible droplet size distribution. It is normally characterized by the "Sauter mean diameter" d_{32} (19) or by the median d_{50} of the size distribution; d_{32} or d_{50}, respectively, have therefore to be regarded as the target quantity of this operation.

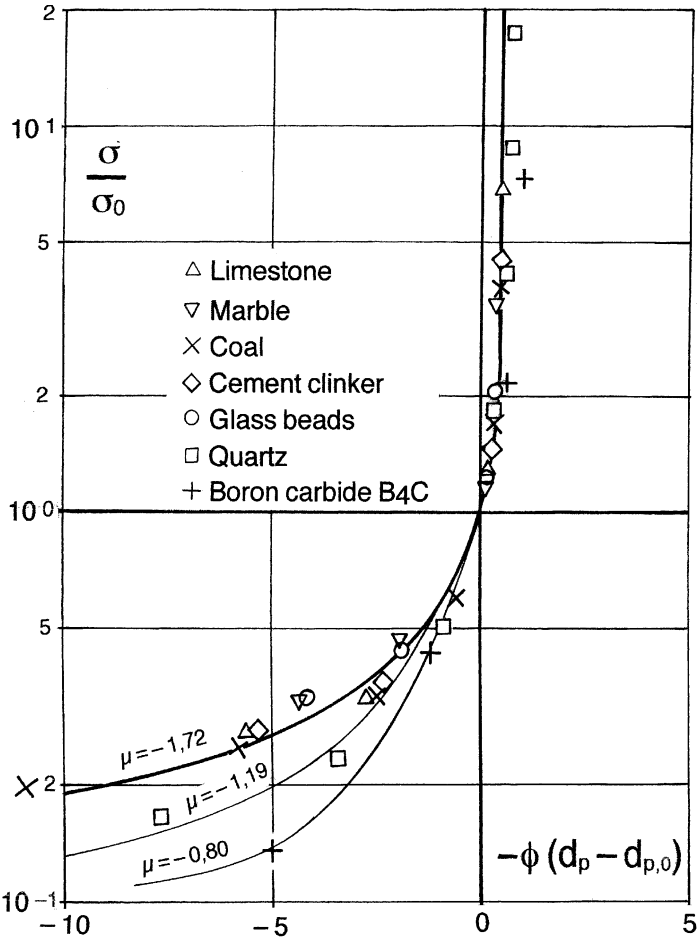

Figure 21 Standard representation of particle strength of various solids as function of particle size. *Source*: From Ref. 23.

The characteristic length of the dispersion chamber, e.g., the slot width between rotor and stator in dispersion mills or the nozzle diameter in high-pressure homogenizers (utilizing high-speed fluid shear), will be denoted as "*d*."

As material parameters, the densities and the viscosities of both phases as well as the interfacial tension σ must be listed. We incorporate the material parameters of the dispersion phase ρ_{d} and μ_{d} in the relevance list and note separately the material numbers ρ/ρ_{d} and η/η_{d}. Additional material parameters are the (dimensionless) volume ratio of both phases ϕ and the mass portion c_i of the emulsifier (surfactant) (e.g., given in ppm).

The process parameters must be formulated as intensive quantities. In appliances where liquid throughput q and the power input P are separated from each other as two freely adjustable process parameters, the volume-related power input P/V and the period of its duration ($\tau = V/q$) must be considered:

$$(P/V)\tau \;=\; E/V \;\left[\mathrm{M\ L^{-1}\,T^{-2}}\right] \tag{66}$$

In appliances with only one degree of freedom (e.g., high-pressure homogenizers), the power is introduced by the liquid throughput. Here, the relevant intensive formulated is therefore power per liquid throughput, P/q. Due to the fact that in nozzles $P \propto \Delta p q$, this results in

$$P/q \;=\; (pq)/q \;=\; p\;\left[\mathrm{M\ L^{-1}\,T^{-2}}\right]. \tag{67}$$

Therefore, the volume-related energy input E/V and the throughput-related power input P/q ($=P$) represent homologous quantities of the same dimension. For the sake of simplicity, Δp will be introduced in the relevance list.

Now, this 6-parametric relevance list of the dimensional parameters (the dimensionless parameters ρ/ρ_d, η/η_d, ϕ, c_{i} are excluded) reads

$$\{d_{32}; d; \rho_d, \eta_d, \sigma; \Delta p\}. \tag{68}$$

The corresponding dimensional matrix

	ρ_d	d	σ	Δp	η_d	d_{32}
M	1	0	1	1	1	0
L	−3	1	0	−1	−1	1
T	0	0	−2	−2	−1	0
M + T/2	**1**	0	0	0	1	0
3M + L + 3 T/2	0	**1**	0	3	2	1
−T/2	0	0	**1**	1	1	2

delivers the remaining three dimensionless numbers:

$$\Pi_1 = \frac{\rho d}{\sigma} = \text{Eu We} = \text{La} \quad \text{(Laplace number)}$$

$$\Pi_2 = \frac{\eta d}{(\rho_d d\sigma)^{1/2}} = \frac{\text{We}^{1/2}}{\text{Re}} = \text{Oh} \quad \text{(Ohnesorge number)}$$

$$\Pi_3 = d_{32}/d.$$

The complete pi set is given as

$$\{d_{32}/d, \text{La}, \text{Oh}, \rho/\rho_d, \eta/\eta_d, \varphi, c_i\} \tag{69}$$

Assuming a quasiuniform power distribution in the throughput or in the volume, a characteristic length of the dispersion space becomes irrelevant. In the relevance list, Equation (66), the parameter d must be cancelled. The target number $\prod_3 \equiv d_{32}/d$ must be dropped and the dimensionless numbers La* and Oh* must be built by d_{32} instead of d. At given and constant material conditions (ρ/ρ_d, η/η_d, φ, $c_i = \text{const.}$), the process characteristics will be represented in the following pi space:

$$\text{Oh}^{*-2} = f\left(\text{La}^*\text{Oh}^{*2}\right)\Phi\ d_{32}\left(\frac{\rho_d\sigma}{\mu_d^2}\right) = f\left\{\Delta p\left(\frac{\mu_d^2}{\rho_d\sigma}\right)\right\} \tag{70}$$

This dependency has been confirmed in two colloid mills in the scale 1:2.2 (24) (Fig. 22). For a material system vegetable oil/water and $\varphi = 0.5$, the following correlation is found:

$$d_{32} = 4.64 \times 10^5 p^{-2/3}, \quad d_{32}(\mu m),\ p\left[\text{M}/\left(\text{LT}^2\right)\right] \tag{71}$$

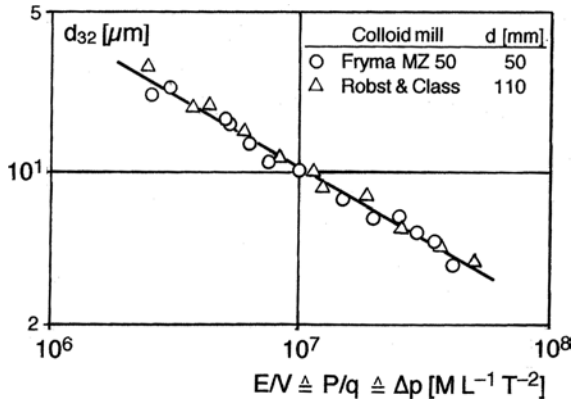

Figure 22 The relationship $d_{32} = f(\Delta p)$ for two colloid mills of different size. Material system: vegetable oil/water and $\varphi = 0.5$. *Source*: From Ref. 24.

Similar results have been presented for other two-parameter appliances (24).

It should be pointed out that the dimensional representations in the form of Equation. (69) as $d_{32} = f(\Delta p)$ present a serious disadvantage as compared to the dimensionless one; Equation (69) is valid only for the investigated material system and tells nothing about the influence of the physical parameters.

Example 11: Fine Grinding of Solids in Stirred Ball Mills

The fine grinding of solids in mills of different shape and mode of operation is used to produce the finest particles with a narrow particle size distribution. Therefore—as in the previous example—the target quantity is the median value d_{50} of the particle size distribution.

The characteristic length of a given mill type is d.

The physical properties are given by the particle density ρ_p, the specific energy of the fissure area β, and the tensile strength σ_Z of the material. Should there be additional material parameters of relevance, they can be easily converted to material numbers by the above-mentioned ones.

The mass-related energy input $E/\rho V$ must be taken into account as a process parameter. The relevance list reads:

$$\left\{ d_{50}; d; \rho_p; \beta; \sigma_Z; E/\rho V \right\} \tag{72}$$

	ρ	d	β	$E/\rho V$	σ_Z	d_{50}
M	1	0	1	0	1	0
L	−3	1	0	2	−1	1
T	0	0	−2	−2	−2	0
M + T/2	**1**	0	0	−1	0	0
3 M + L + 3 T/2	0	**1**	0	−1	−1	1
−T/2	0	0	**1**	1	1	0

From this dimensional matrix the following pi set follows:

$$\{d_{50}/d, (E/\rho V)\rho d/\beta, \sigma_Z d/\beta\} \tag{73}$$

Assuming a quasiuniform energy input in the mill chamber, its characteristic diameter d will be irrelevant. Then the pi set is reduced to

$$\{(E/\rho V)\rho d_{50}/\beta, \sigma_Z d_{50}/\beta\} \rightarrow \; d_{50}(\sigma_Z/\beta) \; = f\{(E/\rho V)(\rho/\sigma_Z)\} \tag{74}$$

In case of unknown physical properties, σ_Z and β, Equation (72) is reduced to $d_{50} = f(E/\rho V)$, which is then used for the scale-up of a given type of mill and grinding material.

For fine grinding of limestone for paper and pottery manufacturing, respectively, bead mills are widely used. The beads of steel, glass, or ceramic have a diameter of 0.2–0.3 mm and occupy up to 90% of the total mill volume ($\varphi \leq 0.9$). They are kept in motion by perforated stirrer discs while the liquid/solid suspension is pumped through the mill chamber. Mill types frequently used are the stirred disc mill, centrifugal fluidized bed mill, and ring gap mill.

Karbstein et al. (26) pursued the question smallest size laboratory bead mill that would still deliver reliable data for scale-up. In differently sized rigs ($V = 0.25$–25 L), a sludge consisting of limestone ($d_{50} = 16\,\mu m$) and 10% aqueous Luviscol solution (mass portion of solids $\phi = 0.2$) was treated. It was found that the minimum size of the mill chamber should be $V = 1$ L. An additional unexpected, but dramatic, result was that the validity of the process characteristics

$$d_{50} \sim (E/\rho V)^{-0.43} \qquad E/\rho V = 10^4 \tag{75}$$

expires at $E/\rho V \approx 10^4$ and the finest particle diameter cannot fall below $d_{50} \approx 1\,\mu m$.

These facts and the scattering of the results made a systematic investigation of the grinding process necessary (27). The grinding process in bead mills is determined by the frequency and the intensity of the collision between beads and grinding medium. According to this assumption, the grinding result will remain constant if these both quantities are kept constant. The intensity of the collision is essentially given by the kinetic energy of the beads:

$$E_{Kin} \sim m_M u^2 \sim V_M \rho_M u^2 \sim d_{M^3} \rho_M u^2 \tag{76}$$

(d_M, ρ_M—diameter and density of the mill beads, u—tip velocity of the stirrer). On the other hand, the frequency depends on the size of the mill chamber and therefore on the overall mass-related energy input. To achieve the same grinding result in differently sized bead mills, as well E_{kin} as also $E/\rho V$ have to be kept idem. The input of mechanical energy can be measured from the torque and the rotational speed of the perforated discs and the kinetic energy can be calculated from Equation (74).

The above assumption was examined with the same material system and the same grinding media (beads). Three differently sized bead mills were used [$V(L) = 0.73$; 5.54; 12.9). Figure 23 shows the results. To achieve a satisfactory correlation, the size of the mill chamber d will have to be introduced in the relevance list. A further finding is that under the same conditions, a smaller mill delivers a coarser product. This had been found already in the previously cited paper (26).

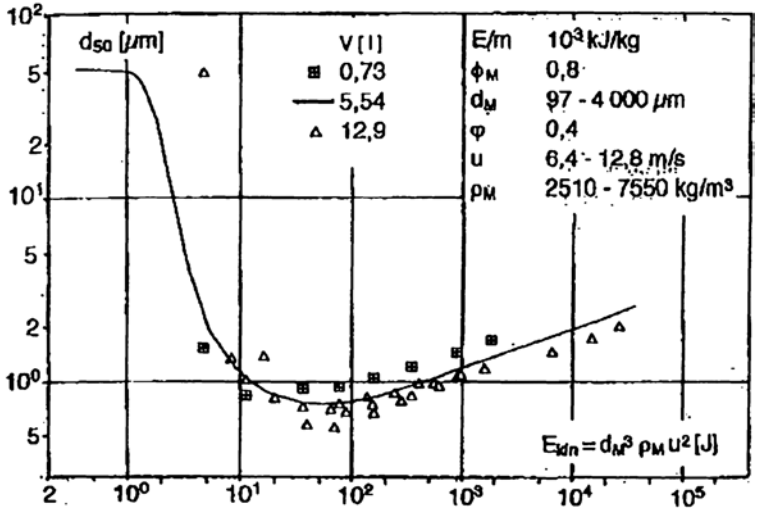

Figure 23 The relationship $d_{50} = f(E_{kin})$ for three colloid mills of same type but different size. Identical material system and constant $E/\rho V = 10^3$ kJ/kg. *Source*: From Ref. 27.

As to the course of the function $d_{50} = f(E_{kin})$ at $E/\rho V = 10^3$ kJ/kg = const., the following explanation is given in Reference 27. With E_{kin} increasing, the particle size first diminishes, but later increases. This is plausible if the introduced specific energy is viewed as a product of the frequency and the intensity of the collision. At $E/\rho V =$ const., and increasing the intensity of the collision, the frequency must diminish, resulting in a coarser product.

APPENDIX

Nomenclature

a	Thermal diffusivity ($\equiv \lambda/\rho C_p$)
A	Surface
c_f	Concentration of foamer and flocculant, respectively
C_p	Heat capacity at constant pressure
d	Stirrer diameter
d_p	Particle or droplet diameter
D	Vessel diameter
D	Diffusivity
F	Force
g	Gravitational acceleration
G	Gravitational constant
l, L	Characteristic length
m	Mass

M	Dimension of mass
n	Rotational speed
p, Δp	Pressure, pressure difference
P	Power
q	Volumetric throughput
R	Universal gas constant
t	(Running) time
T	Dimension of time
v	Velocity
v_s	Velocity of sound
V	Liquid volume

Greek Characters

β	Temperature coefficient of density
	Specific energy of the fissure area in grinding
ϕ	Degree of filling
γ	Temperature coefficient of dynamic viscosity
$\dot{\gamma}$	Shear rate
ν	Kinematic viscosity
μ	Dynamic viscosity
	Scale-up factor ($\mu = l_T/l_M$)
Φ	Volume or mass portion
λ	Thermal conductivity
Π	Dimensionless product
ρ, $\Delta\rho$	Density, density difference
σ	(Interfacial) surface tension
σ_Z	Tensile strength
θ	Period of time
T, ΔT	Temperature, temperature difference
Θ	Dimension of temperature
τ	Residence time; shear stress

Subscripts

G	Gas
L	Liquid
S	Solid
M	Model, laboratory scale
T	Technological, industrial scale

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2

Engineering Approaches for Pharmaceutical Process Scale-Up, Validation, Optimization, and Control in the Process and Analytical Technology (PAT) Era

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The goal of this chapter is to provide a brief overview of standard engineering methods for process development and scale-up and discuss their applicability to the pharmaceutical industry. Model-based design methods and their impact on optimization, scale-up, and process control are discussed. The state of the art is contrasted to a realistic "desirable state" where these methods become part of a new standard of technological articulation.

INTRODUCTION AND BACKGROUND

The time and expense required to develop new drug products are enormous. A recent public food and drug administration (FDA) report (1) estimates that the cost of bringing a new drug to market is between $800 million to $1.7 billion, which represents a 50% increase in just five years (Fig. 1). This cost escalation has very substantial consequences: The number of new drugs and devices submitted to the FDA is dropping rapidly and today it is less than half the number submitted five years ago (Fig. 2). Because of these rising

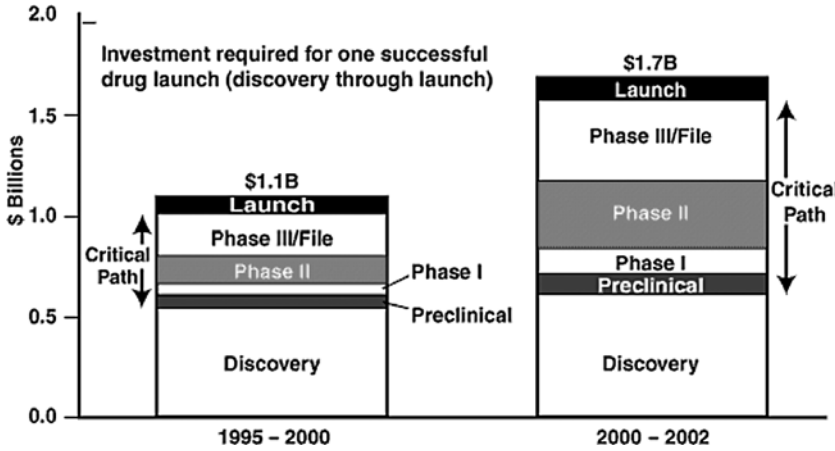

Figure 1 Cost of bringing a new drug to market showing the rapid increase in drug development costs in the last five years. *Source*: From Ref. 1.

costs, innovators concentrate their efforts on products with potentially high market return, and the decreasing pool of new products is one of the main drivers for the recent major wave of mergers and acquisitions across the pharmaceutical industry.

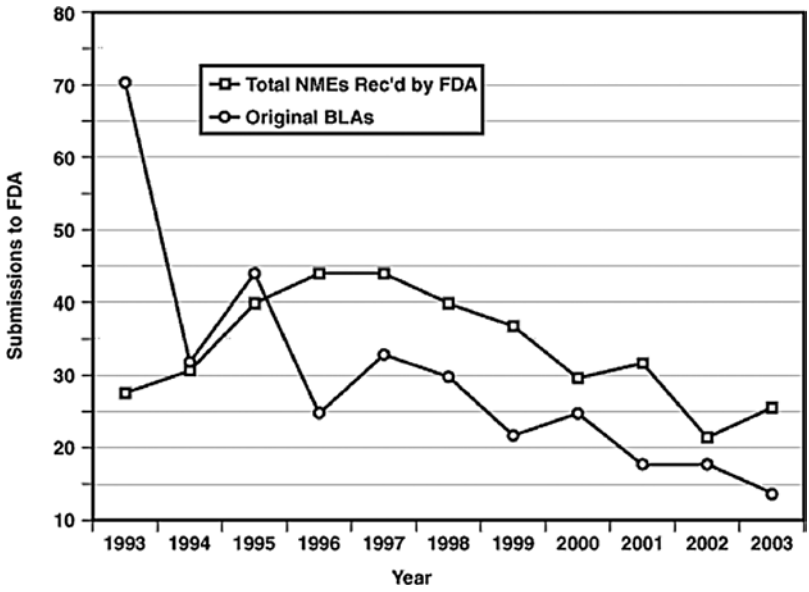

Figure 2 NMEs and BLAs received by the FDA in the last 10 years show the rapid decrease in new products developed. *Abbreviations*: NME, new molecular entities; BLA, biological license application.

The humanitarian cost of this state of affairs is very significant. Many therapies of proven medical efficacy never reach the market because the target disease only affects a "small" population ("orphan drugs"). Therapies for "third world diseases" receive low priority. Development cost is one of the key factors for the rapidly rising costs in health care, which correlates to the growth of uninsured or underinsured populations. The FDA unambiguously identifies the situation as "an impending crisis in public health" caused largely by inadequate product development practices (1).

To invoke a cliché, pharmaceutical product development is an "art" form (Fig. 3) (2). Pharmaceutical products and processes are developed primarily by recipe-driven trial-and-error methods. Typically, the first stage (drug synthesis) yields a drug substance in powder form. In the second stage

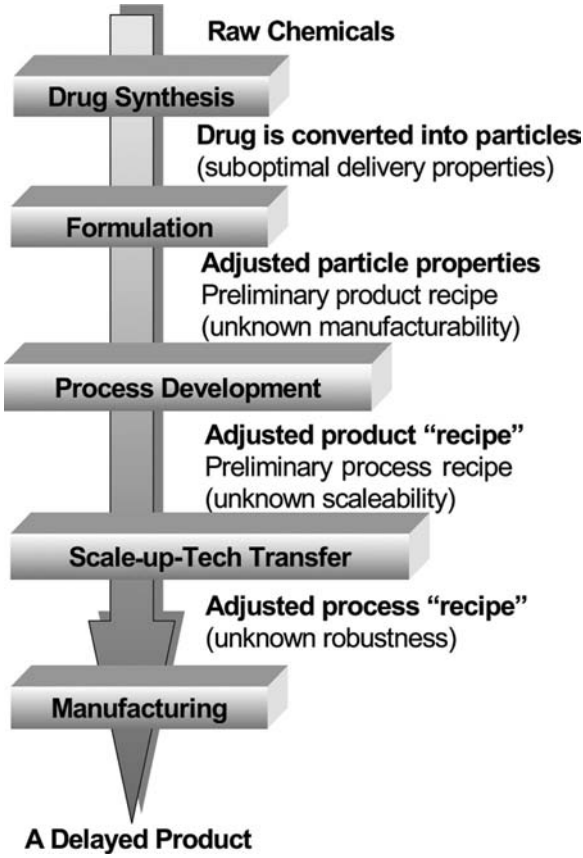

Figure 3 The current product development process, showing the major stages and their outcomes.

(formulation), the material is turned into a preliminary product using small-scale iterative experiments following one of a few available recipes that are expected to achieve the desired release profile (immediate release, delayed release, and sustained release) in a certain environment within the body (stomach, intestine, and colon). In the next stage, the process is scaled-up to a pilot plant, and later on, to manufacturing scale, simply by attempting to replicate the bench-scale recipe in larger-size equipment.

A paucity of predictive science hinders every step of this lengthy and expensive process. Typically, at stage I, the particle properties needed to formulate the material in the desired manner are unknown. At stage II, it is not known how ingredient choices will affect product performance and manufacturability. Later on, scale-up is done simply by attempting to execute the "recipe" using larger equipment. Engineering principles (predictive simulations, dimensional analyses, and scale-up factors) are seldom, if ever, used. Product and process "equivalence" are established a posteriori by examining the product in vivo and in vitro and processing parameters are "tweaked" until the desired performance is achieved.

Once this is accomplished, it is very difficult to introduce changes into the manufacturing process because, simply put, neither industry nor governmental agencies can reliably predict the impact of material or process changes on the final product.

Typically, due to a need to develop the product as quickly as possible, information is transferred only in the downstream direction. This practice significantly hinders true product and process optimization, continuous improvement, and incorporation of new technologies. While in the past this approach might have been tolerable, in recent years these methods are rapidly becoming obsolete. This is due, in part, to significant advances in understanding the genetic basis of disease. New drugs are much more potent (and toxic), requiring very precise manufacturing. They are also increasingly specific, insoluble, chemically vulnerable, and have poor membrane permeability. Thus, they must be delivered in much smaller doses and much more precisely, making product development and manufacturing significantly more difficult, and regulatory expectations much harder to meet. The net result of this rapid progress in drug discovery and this stagnation in process development is an industry where "developers are forced to use the tools of the last century to evaluate this century's advances" (1).

In the author's opinion, the situation just described is not an unavoidable consequence of the intrinsic complexity of pharmaceutical products. In fact, other industries with products that are equally complex (e.g., microelectronics) have developed and implemented predictive methods for product and process development, optimization, and control, capable of much higher quality standards (as defined by allowed variability in product functionality) than the pharmaceutical industry. Rather, current practices in the industry

largely reflect two factors: the business model, which disproportionately rewarded introduction of new products over optimization of existing ones, and the regulatory framework that, for decades, has discouraged innovation and continuous improvement.

Fortunately, as this chapter is written in January 2005, product and process development in the pharmaceutical industry appears to be entering a period of deep transformation, initially driven by recognition at the FDA that a higher technological standard was a desirable and achievable goal, and fueled by an intense desire for improvement on the part of many industrial scientists and engineers.

Let us describe the desired future state of pharmaceutical product and process development by comparison to another industry: airplane construction. The design of an airplane begins with the selection of its desired performance, i.e., we wish to build a device capable of flying at a given speed, carrying a given load, while optimizing cost (e.g., fuel consumption). The laws of aerodynamics are then invoked in developing predictive computer models that are used to design and optimize the structure of the intended airplane before a single piece is ever built. A small-scale model is then constructed and tested under conditions that are predictive of the performance of the full-scale device (e.g., a wind tunnel operated under specifically selected conditions). Once theory is verified by experiment, the final product is built, and it performs as intended (or very close to it).

We would be hard-pressed to accept a situation where airplane development was conducted by the methods used in 1903 by the Wright brothers, i.e., by building many aircrafts, all slightly different, and testing them in the field in order to select for subsequent use those that perform appropriately (i.e., those that did not crash). Yet, in essence, that is how pharmaceutical products are developed. At the present time, a formulation/manufacturing method is proposed, tried in the field, and retained if the product performs as intended, otherwise it is slightly modified, tried again, and so on. A whole century of model-based product and process design has somehow gone largely unnoticed.

Far from being unique to the aerospace industry, model-based design and optimization are standard practice across a great many industries, including microelectronics, petrochemicals, and automobiles. All of these industries share four characteristics:

- materials used to build products are well understood and their performance is predictable
- the fundamental laws that govern product and process performance across scales are known, and have been articulated in the form of predictive mathematical models
- model-based methods for product and process design, optimization, and control have been developed and tested

- a human resource skilled in the use of such methods has been developed and incorporated into organizational structures that take full advantage of their capabilities

In the author's view, these four characteristics summarize the desired (and achievable) state of product and process design and development in the pharmaceutical industry. These views are largely espoused by the FDA (3), which in recent regulatory language has defined "process understanding" (now accepted to be the central goal of the Process Analytical Technology Initiative) as the ability to predict performance (4). Much has been said and written about the evolving regulatory views, and a review of the discussion is not warranted here; rather, the reader is encouraged to visit the FDA Web site (5) and review the documentation posted there. Instead, in the remainder of this chapter, we focus on providing an engineering perspective for achieving the above mentioned desired state.

The chapter is organized as follows. First, to establish a common language, we define some common terms from both a pharmaceutical and an engineering perspective. Subsequently, we review model-based design and optimization as a framework for product and process development and optimization, process scale-up, and continuous improvement activities. The role of process and analytical technology (PAT) methods and principles in this framework is discussed. Finally, the main areas requiring effort are identified.

MODEL-BASED OPTIMIZATION

Certain engineering terms are often used in industrial pharmacy practice with a loose meaning, generating significant confusion. Consider, for example, the term *optimization*, which in industrial pharmacy often refers to the practice of examining process performance empirically, for a small set of parameter values often chosen based on experience (such as three different blending times) and then selecting the value that gives the results that are deemed most adequate. The choice is often made without resorting to statistical comparison of results. *Scale-up* refers to a process development stage (Fig. 3) where the process recipe is carried out in larger equipment, and scale equivalence is "established" by demonstrating the ability to manufacture adequate product. A process is said to be *in control* when it is possible to make many batches of product within specification.

To an engineer, these terms have radically different meanings. Optimization is the use of a predictive model to determine the best possible design of a product, or the best possible operating condition for a process. To find "the best," the design space (the permissible region of parameters given technical, regulatory, or economic constraints) is identified. A quantitative target function describing the property to be optimized is developed. The target function can be a single performance attribute (quality, technical

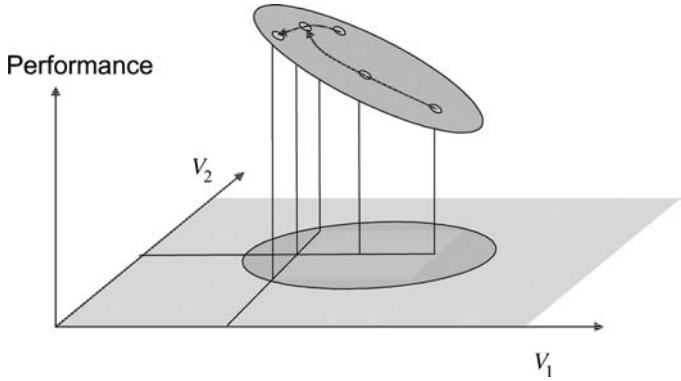

Figure 4 Schematic of the model-based optimization process, where performance depends on two variables (V_1 and V_2). Model-based methods would explore the entire oval domain, seeking the "global best." Common OVAT practices only explore a few points along orthogonal trajectories. *Abbreviation*: OVAT, one variable at a time.

performance, and profit), or a combination of multiple parameters after they are assigned a given weight. Once the design space and the target function are known, the absolute minimum (or maximum) of this function is found (Fig. 4).

Typically, the optimization process is conducted in iterative fashion (Fig. 5), beginning with the development of a model of the process. The model can be statistical (6) or mathematical. In early stages of product or process design, relatively little is known, and only a preliminary version of

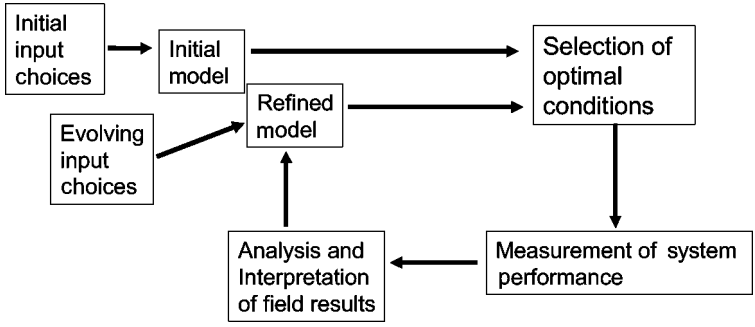

Figure 5 The iterative optimization process. An initial model is developed, used to predict process performance, tested by comparison with experiment, refined, and used to improve prediction. The process naturally accommodates changes in economic or regulatory constraints.

the model can be developed. A "first pass" optimization exercise is conducted. Model predictions are compared with actual performance, and results are used to improve the model itself. Results are also used to refine knowledge about design space boundaries. The more refined model is used to generate higher quality performance predictions, which are again used to predict an optimum operating regime. Comparisons of prediction and practical observations are used to further improve the model, the target function, and the design space. The process continues ad infinitum following a virtuous cycle that leads to ever better predictive power.

Since economic conditions, process capabilities, and regulatory requirements change over time, both the design space and the target function are dynamic structures, and the optimum product or process design is, in fact, a moving target. Model-based optimization is ideally suited to respond to these dynamics. Once a high-quality model is available, the change in conditions can be incorporated into the process, and a new iteration along the virtuous cycle is performed to generate the new selection of optimum processing conditions.

Oil refining is perhaps the best-developed example of a process operated in this "continuous optimization mode." A refinery receives a different mixture of petroleum every day, and the prices of its various products fluctuate continuously. Exquisite knowledge of the process is used to determine the precise conditions (temperatures, pressures, recycle rates, etc.) that would product the optimum product mix for the available raw materials and market conditions. As the factory is operated, model predictions are compared to actual performance, and deviations are used to optimize model performance.

True optimization process can be challenging. The design space can be a complex, irregularly shaped region (or set of disconnected regions) in an n-dimensional space. The target function can have local minima that can "trap" the trajectory of the solution-seeking algorithm. To avoid such "non-convex" situations, searching algorithms have been developed that incorporate a certain measure of randomization in the sequential selection of process conditions to be examined. Ample literature exists on the topic and is not reviewed here in the interest of brevity; for an introduction, see References (7,8).

Current practices in industrial pharmacy can now be put in perspective. Typically, the method of choice is univariate one variable at a time (OVAT). One variable is examined for a few conditions, which, in practice, are selected within a "safe" subset of the permissible design space. A value of this parameter is selected and kept subsequently constant. Another variable is then examined, a value is chosen, and the process continues sequentially. Intuitively, unless the target function is essentially a plane, if the end result is anywhere near the global optimum, it is only by chance. A historical reason for this dated practice is that the regulatory framework greatly discouraged implementation of the virtuous cycle mentioned above, which

is the heart of the optimization process. Once a process was approved, the cost of implementing improvements (and the risk of examining process performance outside approved sets of parameters) was simply too high. As a result, while the rest of the industrial world embarked in wave after wave of quality revolutions, pharmaceutical process development practices stayed frozen in decades-old paradigms from a time before computer models.

PROCESS SCALE-UP

Development of PAT approaches for process scale-up is likely to take place at several levels. At the conceptually simplest level, PAT presupposes the development of sensing instruments capable of monitoring process attributes online and in real time.

Once the analytical method is validated for accuracy at the laboratory scale, it can be used to obtain extensive information on process performance (blend homogeneity, granulation particle size distribution, and moisture content) under various conditions (blender speed, mixing time, drying air temperature, humidity, volume, etc.). Statistical models can then be used to relate the observable variables to other performance attributes (e.g., tablet hardness, content uniformity, and dissolution) in order to determine ranges of measured values that are predictive of acceptable performance.

Typically, for batch processes such as blending or drying, this entails the determination of process end-point attributes. The PAT method then becomes the centerpiece of the scale-up effort. Process scale-up can be undertaken under the assumption that the relationships between observables and performance are independent of scale, and if this assumption is verified in practice, the manufacturing process in full scale can be monitored (typically, to completion) providing a higher level of assurance that the product is likely to be within compliance.

For continuous or semi-continuous processes (such as tablet compression), the main role of PAT methods is not process end-point determination; rather, it is to serve as a component of a feedback or feed-forward control strategy devoted to keeping process (and product) performance within the desired range along the life of the process. This is conceptually more complex and requires a greater level of predictive understanding regarding the dynamic effect of controlled variables on performance attributes (see below). However, once the development of suitable controls is achieved, scale-up itself is greatly simplified for continuous (or semi-continuous) processes, typically involving running the process for longer times.

At a more sophisticated level of articulation, PAT will involve the use of analytical methods, coupled with modeling approaches, to develop models capable of quantitatively predicting the relationship between input parameters (raw material properties, process parameters, and environmental input) and product performance. In the author's opinion, this is the true

definition of "process understanding." At an early stage, models can be statistical (correlation-based), seeking only to determine directional relationships and covariances. Over time, predictive mathematical models can be developed, once mechanistic relationships between inputs and outputs are established.

Predictive models make it possible to perform true process scale-up, which consists of the use of a predictive model to find quantitative criteria for establishing process similarity across scales. The model is also used to determine the changes in both the design space and the target function across scales, and to predict optimum conditions of manufacturing facilities yet to be built.

Even more, a predictive model allows the designer to explore beforehand the effect of uncertainty in raw material properties, market conditions, and regulatory constraints, thus making it possible to design flexible manufacturing systems that have built-in capabilities for accommodating changing conditions. The methodology known as "design under uncertainty" is currently an active area of research in the systems engineering community.

PROCESS CONTROL

As mentioned above, process control entails monitoring a process continuously, and whenever necessary, taking corrective action (by acting on controlled variables) in order to keep the system under control. While a large number of control strategies have been developed and studied (9,10), in essence all control systems involve the same components (Fig. 6): (a) instrumentation capable of measuring on-line, in real time, the values of controlled variables, input parameters (e.g., environmental variables, process inputs), and process conditions, (b) a set of specifications for the desired process conditions, (c) a predictive model describing the effect of controlled variables on process conditions, and (d) a control policy prescribing the manner in which controlled variables must be modified in response to measured deviations in either input parameters or process conditions.

Two main control schemes exist: feedback control and feed-forward control (Fig. 6). In feedback control (by far the most common), system performance is monitored, deviations from desired conditions are quantified, and controlled variables are modified to return the system to the desired state. In feed-forward control, process inputs are monitored. As they deviate from desired values, their effect on the system is predicted, and controlled variables are modified to minimize their effect. Feedback control is "safer," since it guarantees performance by controlling it directly, but it is also slower; corrective action is taken only after the perturbation has affected process performance. Feed-forward control is faster; it acts on input deviations as soon as they are detected. However, it is riskier; if the detected

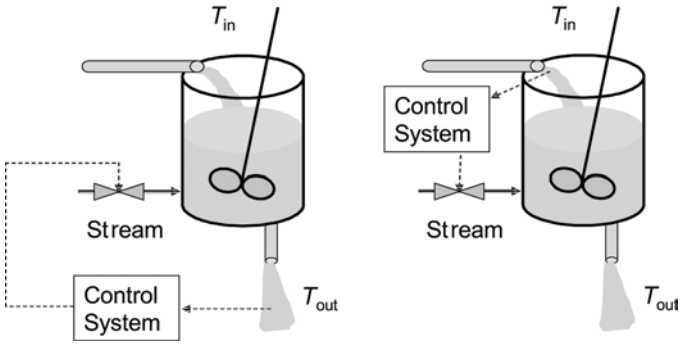

Figure 6 Schematic of a control system, using a stirred tank as an example. A stream enters the tank at temperature T_{in}. The system is designed to maintain the exit temperature at T_{out}. In a feedback mode, the exiting temperature is measured and the stream feed is opened or closed as necessary. T_{out} is known, but the effects of variability are corrected only after they have entered the system. In a feed-forward mode, the incoming temperature is measured and the stream feed is modified to prevent its variability from entering the system. However, T_{out} is unknown.

deviation is a measurement error, the control system will purposefully move the system away from the desired set-point.

It is apparent that a predictive model is the hearth a control algorithm. Unless the relationship between process inputs and process performance is known, deviations can be detected, but effective corrective action cannot be taken. However, fast, error-free monitoring is also essential: unless inputs and state variables can be quickly and accurately quantified, the control system is blind and devoid of value.

As with scale-up, two levels of implementation are possible. The first level only entails the ability to sense, and a directional characterization of the effect of variables. PAT methods can be extremely effective for this purpose by generating large datasets of process inputs and outputs that can then be correlated to generate statistical or polynomial control models. Provided that (*i*) deviations from desired set-points are small, (*ii*) interactions between inputs are weak, and (*iii*) the response surface does not depart too much from linearity, such systems can provide the basis of an initial effort to control a system.

However, for many systems, more sophisticated control systems capable of overcoming these restrictions are likely to be desirable. To develop such systems, we need to expand the predictive models mentioned above to incorporate the ''dynamic'' effects of input, control, and process variables. The model needs to be able to answer questions such as how quickly do deviations in input conditions propagate through the system, how does the system respond over time under different control policies, and what is the

effect of lags in sensing and responding. The control system itself becomes part of these dynamics; depending on the control policy, the response of the system as a whole will be different. Moreover, the model can be used to optimize the control system by allowing the user to determine the optimum number and location of the sensing points, the ideal control policy for a given system, etc. Since lags, capacities, and propagation rates are almost always scale-dependent, the control system developed under laboratory conditions needs to be adjusted in the scaled-up version of the system. The outcome, however, is highly desirable: a system where variability sources are known, understood, and managed.

CONCLUSIONS

This brief chapter summarized some of the main roles of PAT for process optimization, scale-up, and control. In the author's view, the development of models capable of predicting the effects of raw material properties and process parameters on process performance is not only desirable, but also a highly necessary condition for the development of modern approaches for optimal design and control of manufacturing processes. Given the complexity and diversity of materials and products and the tight quality requirements, the task might appear to be daunting. However, it is an achievable task, as demonstrated by the daily track record of other industries that deal with highly complex products and processes. An important reason is that generic process models usually only need to be developed once; the better the model, the more universal it will be.

Arguably, given its immediate and direct impact on public health, the pharmaceutical industry has additional reasons to achieve a higher level of technological execution where product quality is assured by effective automated systems and where variability sources are understood and minimized. Even removing this motivation, this industry should embrace model-based optimization enthusiastically, since it has reduced cost and accelerated product development across many other industries.

In the last two years, recognition of the need to achieve the goals described here have motivated an active dialogue between regulatory agencies, pharmaceutical companies, and academia. Recognition is emerging that sustained efforts and substantial resources will be needed in years to come. It is also becoming clear that the path ahead is no longer optional; a consensus has emerged that the state-of-the-art is inadequate and that positive change is possible.

An important final thought is that substantial efforts need to be made in the development of properly trained human resources both at companies and at regulatory agencies. Application of the methods mentioned in this chapter requires a substantial level of expertise that has not been part of the traditional training of industrial pharmacists and chemists, and

engineers have, by and large, not been integrated into product development teams at companies or in regulatory bodies.

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3

A Parenteral Drug Scale-Up

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INTRODUCTION

The term "parenteral" is applied to preparations administered by injection through one or more layers of skin tissue. The word is derived from the Greek words para and etheron, meaning outside of intestine, and is used for those dosage forms administered by routes other than the oral route. Because administration of injectables, by definition, requires circumventing the highly protective barriers of the human body, the skin and the mucus membranes, the purity of the dosage form must achieve exceptional quality. This is generally accomplished by close utilization of good manufacturing practices.

The basic principles employed in the preparation of parenteral products do not vary from those widely used in other sterile and non-sterile liquid preparations. However, it is imperative that all calculations are made in an accurate and most precise manner. Therefore, an issue of a parenteral solution scale-up essentially becomes a liquid scale-up task, which requires a high degree of accuracy. A practical yet scientifically sound means of performing this scale-up analysis of liquid parenteral systems is presented below. The approach is based on the scale of agitation method. For single-phase liquid systems, the primary scale-up criterion is equal liquid motion when comparing pilot-size batches to a larger production-size batches.

One of the most important processes involved in the scale-up of liquid parenteral preparations is mixing (1). For liquids, mixing can be defined as a

transport process that occurs simultaneously in three different scales during which one substance (solute) achieves a uniform concentration in another substance (solvent). On a large, visible scale, mixing occurs by bulk diffusion in which the elements are blended by the pumping action of the mixer's impeller. On the microscopic scale, elements that are in proximity are blended by the eddy currents, and they form drag where local velocity and shear-stress differences act on the fluid. On the smallest scale, final blending occurs via molecular diffusion whose rate is unaffected by the mechanical mixing action. Therefore, large-scale mixing primarily depends on flow within the vessel, whereas small-scale mixing is mostly dependent on shear. This approach focuses on large-scale mixing using three viable approaches, specifically concentrating on the scale-of-agitation method.

GEOMETRIC SIMILARITY

There are several methods to achieve appropriate scale-up of mixing. The first method involves geometric similarity. This technique employs proportional scale-up of geometric parameters of the vessel. The scaled-up parameters may include such geometric ratios as D/T ratio, where D is diameter of the impeller and T is diameter of the tank, and Z/T ratio, where Z is the height of the liquid in the vessel. Similar ratios are compared for both the small-scale equipment (D_1T_1) and the larger size equipment (D_2T_2). For example,

$$R = D_1T_1 = D_2T_2 \tag{1}$$

where R is the geometric scaling factor.

After R has been determined, other required parameters such as the rotational speed of the larger equipment can then be calculated by power law relationships. In the above example, the required rotational speed, N, can be calculated as

$$N_2 = N_1\left(\frac{1}{R}\right)^n \tag{2}$$

Rotational speeds may be expressed either in terms of rpm or in terms of hertz. The power law exponent, n, has a definite physical significance. The value of n and the corresponding significance are determined either empirically or through theoretical means. Table 1 lists the most common values assigned to n.

Scale-up can be completed by using predicted values of N_2 to determine the horsepower requirements of the large-size system. In most designs, D/T will be in the following range:

$$0.15 \leq \frac{D}{T} \leq 0.6 \tag{3}$$

Table 1 Most Common Values Assigned to the Power Law Exponent, n, When Comparing Large- to Small-Scale Equipment

n	Physical interpretation
0	Equal blend time This exponent is rarely used due to excessively large equipment requirement to hold speed constant
1/2	Equal surface motion Equal surface motion is related most often to vortex formation. The depth of the vortex is related by geometric similarity and equal Froude number: $N_{\mathrm{Fr}} = DN^2/g$
2/3	Equal mass transfer rates Scale-up based on the mass-transfer rate between phases is directly related to liquid turbulence and motion at the interface. Scale-up of solids dissolution rate or mass transfer between liquid phases is adequately handled utilizing 2/3 as an exponent
3/4	Equal solids suspension Agitation for a desired level of solids suspension is based on an overall appearance of the solid–liquid system. Results of the empirical correlations have been summarized for most types of solids-suspension scale-up cases
1	Equal liquid motion (equal average fluid velocity) Analyzing the significance of the scale-up exponent for liquid motion shows that the similar results are obtained when equal tip speed (fluid velocity) of torque per volume is applied to geometrically similar agitation system

and Z/T will be in the range:

$$0.3 \leq \frac{Z}{T} \leq 1.5 \tag{4}$$

These values, in conjunction with N and the horsepower requirements, may completely define the major parameters of the systems. However, in most of the cases, scaled-up bench batches yield atypical agitator speeds and significantly larger power requirements. The number of ANSI/AGMA agitator speeds and standard motor horsepowers available off-the-shelf is quite sufficient to closely approximate most levels of agitation. It is very seldom that the level of agitation of scaled liquid system requires a non-standard agitator. Upon identification of the RPM and horsepower requirements, the scale-up procedure continuous to the engineering and economic evaluation phase. For illustration purposes, equal power per volume with geometric similarity is shown to be equivalent to a scale-up exponent of $n = 2/3$. Turbulent power

requirement or a constant power number is proportional to the product of agitator speed subbed and diameter of the impeller diameter to the fifth power:

$$P \propto N^3 D^5 \tag{5}$$

Due to the geometric similarity conventions that hold all length ratios constant, tank dimensions are a fixed multiple of impeller diameter. Therefore, the tank volume is proportional to impeller diameter cubed:

$$V \propto D^3 \tag{6}$$

Subsequently, if power per volume is held constant in two different size systems, the agitator speed must change in relation to the impeller diameter:

$$P/V \propto N^3 D^2 \tag{7}$$

$$N_1^3 D_1^2 = N_2^3 D_2^2 \tag{8}$$

Rearranging Equation (8) into Equation (2) demonstrates that this relationship is equivalent to a scale-up exponent of two-thirds:

$$N_2 = N_1 \left(\frac{D_1}{D_2}\right)^{2/3} = N_1 \left(\frac{1}{R}\right)^{2/3} \tag{9}$$

It is important to note that the small-scale agitator operations may be described in terms of impeller diameter and agitator speed, while manufacturing process equipment is more conveniently specified by horsepower and fluid velocity. For most standard turbine configurations, power number correlations are available to convert impeller diameter and agitator speed into a horsepower value for given fluid properties. Most laboratory bench equipment is designed to provide a torque measurement that can be readily converted to horsepower directly from the conditions of the pilot batches.

DIMENSIONLESS NUMBERS METHOD

The second method uses dimensionless numbers to predict scale-up parameters. The use of dimensionless numbers simplifies design calculations by reducing the number of variables to consider. The dimensionless number approach has been used with good success in heat transfer calculations and to some extent in gas dispersion (mass transfer) for mixer scale-up. Usually, the primary independent variable in a dimensionless number correlation is Reynolds number:

$$N_{\mathrm{Re}} = \frac{D^2 \rho N}{\mu} \tag{10}$$

where N is the shaft speed (per second), D the propeller blade diameter (cm), ρ the density of the solution-dispersion (g/cm^3), and μ is the viscosity of the solution-dispersion (g/cm/sec).

Other dimensionless numbers are widely used for various scale-up applications. One example is Froude number:

$$N_{\mathrm{Fr}} = \frac{DN^2}{g} \tag{11}$$

where g is acceleration due to gravity in cm/sec. The Froude number compares inertial forces to gravitational forces inside the system.

Another example is the power number, which is a function of the Reynolds number and the Froude number:

$$N_{\mathrm{p}} = \frac{Pg_{\mathrm{c}}}{\rho N^3 D^5} \tag{12}$$

where P is power and g_{c} is a gravitational conversion factor. This number relates density, viscosity, rotational speed, and the diameter of the impeller. The power number correlation has been used successfully for impeller geometric scale-up. Approximately half a dozen other dimensionless numbers are involved in the various aspects of mixing, heat and mass transfer, etc.

Both of the above methods belong to a traditional fluid mechanical approach known as dimensional analysis (2). Unfortunately, these methods cannot always achieve results in various manufacturing environments. Therefore, the third method is introduced below and can be easily applied to various research and production situations. This method actually is a combination of the first two methods.

SCALE-OF-AGITATION APPROACH

The basis of the scale-of-agitation approach is a geometric scale-up with the power law exponent, $n = 1$ (Table 1). This provides for equal fluid velocities in both large- and small-scale equipment. Furthermore, several dimensionless groups are used to relate the fluid properties to the physical properties of the equipment being considered. In particular, bulk-fluid velocity comparisons are made around the largest blade in the system. This method is best suited for turbulent flow agitation in which tanks are assumed to be vertical cylinders.

Although high success may be achieved in applying this technique to marine-type propeller systems, the original development was based on low-rpm, axial, or radial impeller arrangements. Because the most intensive mixing occurs in the volume immediately around the impeller, this discussion focuses on this particular region of mixing. Table 2 describes the nomenclature used to develop the theory behind the approach.

The analysis proceeds as follows. First, determine the D/T ratio of the tank, based on the largest impeller, in which the original (usually research and development) batches had been compounded. It is also necessary to know the rotational speed and the horsepower of the mixer used.

Table 2 Nomenclature

Q	Effective pumping capacity or volumetric pumping flow in cm^3/sec
N	Shaft speed in per second
N_{RE}	Impeller Reynolds number, dimensionless
N_Q	Pumping number, dimensionless
D	Diameter of the largest mixer blade in cm
ρ	Density of the fluid in g/cm^3
μ	Viscosity of the fluid in g/cm/sec
ν_b	Bulk fluid velocity in cm
T	Diameter of the tank in cm
A	Cross-sectional area of the tank in cm^2

The only two product physical properties needed are density and viscosity. Generally, parenterals, as the most solution-type products, will follow Newtonian fluid behavior and may also be considered incompressible. Therefore, point densities and viscosities can be used satisfactorily.

The next step in the analysis is to calculate the impeller Reynolds number achieved during this original compounding using Equation (12). The impeller Reynolds number must be >2000 to proceed with analysis (3).

Mixing achieved in the initial research and development processing must be in turbulent range. If the impeller Reynolds number is <2000, then mixing in the pilot tank was either inadequate or represented some other special case such as moderately viscous fluids. In these situations, another D/T ratio curve must be used.

Proceeding further, obtain the value of the terminal pumping number in the R&D pilot process by using the following formula:

$$N_Q = 1.1283 - \left[1.07118\left(\frac{D}{T}\right)\right] \tag{13}$$

Equation 13 is the empirical relationship obtained by the linear regression between D/T and terminal pumping numbers (4). It is important to note that a family of curves exists for each D/T ratio when N_Q (pumping number) is plotted versus the impeller Reynolds number (5). In the turbulent range ($N_{Re} > 2000$), the N_Q curves flatten out and thus are independent of the Reynolds number.

The terminal pumping number, $N_{Q/Re} > 2000$, plotted against the D/T ratio results in Equation (13).

The cross-sectional area of the pilot-size tank is determined by using Equation (14).

$$A = \frac{\pi T^2}{4} \quad (cm^2) \tag{14}$$

Table 3 Process Requirements Set Degree of Agitation for Blending and Motion

Scale of agitation	Bulk fluid velocity (cm/sec)	Description of mixing
1	3	Agitation levels 1 and 2 are characteristic of applications requiring minimum fluid velocities to achieve the product result.
2	6	Agitators capable of level 2 will: Blend miscible fluids to uniformity, if specific gravity differences are less than 0.1 and if the viscosity of the most viscous is less than 100 times the viscosity of the other; Establish complete fluid batch control; Produce a flat, but moving fluid-batch surface.
3	9	Agitation levels 3 to 6 are characteristic of fluid velocities in most chemical (including pharmaceutical) industries' agitated batches.
	12	Same as 3
5	15	Same as 3 and 4
6	18	Agitators capable of level 6 will: Blend miscible fluids to uniformity, if specific gravity differences are less than 0.6 and if the viscosity of the most viscous is less than 10,000 times the viscosity of the other; Suspend trace solids (<2%) with settling rates of 2–4 ft/min; Produce surface rippling at lower viscosities.
7	21	Agitation levels 7–10 are characteristic of applications requiring high fluid velocities for process result, such as mixing of the high viscosity suspension preparations.
8	24	Same as 7
9	27	Same as 7 and 8
10	30	Agitators capable of level 10 will: Blend miscible fluids to uniformity, if specific gravity differences are less than 1.0 and if the viscosity of the most viscous is less than 100,000 times the viscosity of the other; Suspend trace solids (<2%) with settling rates of 4–6 ft/min; Provide surging surface at low viscosities.

Then, the value of effective pumping capacity for the pilot-size mixer is calculated using Equation (15).

$$Q = N_Q N D^3 \quad (\text{cm}^3/\text{sec}) \tag{15}$$

Finally, by inserting the values derived in Equations (14) and (15) into Equation (16), the value for bulk fluid velocity around the largest impeller of the system is obtained.

$$\nu_b = \frac{Q}{A} \quad (\text{cm/sec}) \tag{16}$$

The bulk fluid velocity can be inserted into Table 3 to determine the level of agitation achieved in the original R&D pilot batch. The larger size production tank and mixer are then designed so that the scale of agitation produced in the larger vessel matches that required for the pilot-size batches. The scale-of-agitation approach was first developed in the mid-1970s by engineers at Chemineer Inc. (6).

Table 3 summarizes the scale-of-agitation parameters and gives a qualitative description of the type of mixing associated with the various levels. According to this approach, mixing is a similar process if the calculated bulk fluid velocities for the production-size vessels lie within ± 1 unit level of the scale of agitation required from an analysis of the R&D pilot batches. It is quite easy to match the required scale of agitation by simply adjusting the revolutions per minute when working with a variable-speed equipment. Thus, a given tank equipped with a variable-speed mixer will generally be capable of several agitation levels.

SCALE-OF-AGITATION APPROACH EXAMPLE

To illustrate the actual application of the scale-of-agitation approach to scale-up, the above method was applied to the scale-up of typical injectables solution from 378-L pilot batch to a 3780-L production-size batch. The example product is a Newtonian fluid with density of 1.018 g/cm^3 and a viscosity of 0.0588 g/cm/sec (5.88 cps). The tank used in the manufacturing of the pilot batch had the following parameters:

T = diameter of the tank = 74.6 cm
A = cross-sectional area = 4371 cm^2

The agitation was accomplished with the turbine-type mixer and the largest axial impeller was 40.64 cm. The pilot batch was mixed at 90 rpm (1.5/sec). From the initially known data, the D/T ratio was determined.

$$\frac{D_{378\,\text{L}}}{T_{378\,\text{L}}} = \frac{40.64\,\text{cm}}{74.60\,\text{cm}} = 0.54 \tag{17}$$

Then the value of the impeller Reynolds number was obtained by plugging known values into Equation (5).

$$N_{\mathrm{Re}(3785\,\mathrm{L})} = \frac{D_{378\,\mathrm{L}}^2 \rho N_{378\,\mathrm{L}}}{\mu} = \frac{(40.64\,\mathrm{cm})^2(1.018\,\mathrm{g/cm^3})(1.5\,\mathrm{per\,sec})}{0.0588\,\mathrm{g/cm/sec}} = 44,449 \tag{18}$$

Because the value of the Reynolds number is >2000, Equation (13) is used to obtain the pumping number. The pumping number is inserted into Equation (15) to obtain the effective pumping capacity.

$$Q_{378\,\mathrm{L}} = (N_{\mathrm{Q}(378\,\mathrm{L})})(N_{378\,\mathrm{L}})(D_{378\,\mathrm{L}}^3) = (0.55)(1.5\,\mathrm{per\,sec})(40.64\,\mathrm{cm})^3 = 55,375\,\mathrm{cm^3/sec}. \tag{19}$$

Knowing the effective pumping capacity of agitation and crosssectional area of the pilot-batch tank, bulk fluid velocity is obtained by using Equation (16).

$$\nu_{\mathrm{b}(378\mathrm{L})} = \frac{Q_{378\,\mathrm{L}}}{A_{378\,\mathrm{L}}} = \frac{55,375\,\mathrm{cm^3/sec}}{4371\,\mathrm{cm^2}} = 12.6\,\mathrm{cm/sec} \tag{20}$$

Inserting this bulk fluid velocity into Table 3, one can calculate the level of agitation used in the pilot batch of indictable solution as 4, which is described as characteristic of fluid velocities in most chemical process industries' agitated batches.

Now the appropriate shaft speed for scaled-up production equipment can be calculated. The tank used for production batches has a capacity of 3780 L. It is equipped with a turbine-type agitator that has a shaft speed range of 20–58 rpm. The diameter of this tank is 167 cm. The diameter of the largest axial impeller is 87 cm. Given the diameter of the production tank, the cross-sectional area can be determined as

$$A_{3780\,\mathrm{L}} = \frac{\pi T_{3780\,\mathrm{L}}^2}{4} = \frac{\pi(167\,\mathrm{cm})^2}{4} = 21904\ \mathrm{cm^2} \tag{21}$$

The next step is solving Equation (15) for effective pumping capacity in the larger vessel.

$$Q_{3780\,\mathrm{L}} = (\nu_{\mathrm{b}(378\mathrm{L})})(A_{3780\,\mathrm{L}}) = (12.6\,\mathrm{cm/sec})(21,904\,\mathrm{cm^2}) = 2,75,990\,\mathrm{cm^3/sec} \tag{22}$$

Earlier, the analysis established that the mixing of this product occurs in the turbulent flow regime because the Reynolds number obtained far exceeds

minimally required 2000. Therefore, the pumping number can be calculated for 3780-L tank by using Equation (14) to obtain

$$N_{Q(3780\,L)} = 1.1283 - \left[1.07118\left(\frac{87\,\text{cm}}{167\,\text{cm}}\right)\right] = 0.57 \tag{23}$$

Finally, Equation (16) is rearranged to solve for appropriate shaft speed to be used in a 3780-L batch.

$$N_{3780\,L} = \frac{Q_{3780\,L}}{N_{Q(3780\,L)} D_{3780\,L}^3} = \frac{2,75,990\,\text{cm}^3/\text{sec}}{(0.57)(87\,\text{cm})^3} = 0.73\,\text{per sec} = 44\,\text{rpm} \tag{24}$$

The shaft speed value obtained is well within the rpm range of the 3780-L tank agitator. To determine the rpm range for production batches, start with level-3 agitation at the low rpm end and level-5 agitation at the high rpm end. Table 3 provides bulk velocities for levels 3 and 5. In turn, these are used to calculate the respective pumping capacities, defined via Equation (16). The low and high speeds are then calculated, as described above, by rearranging Equation (15).

This method can be easily used to show the logic behind the scale-up from original R&D batches to production-scale batches. Although scale-of agitation analysis has its limitations, especially in mixing of suspension, non-Newtonian fluids, and gas dispersions, similar analysis could be applied to these systems, provided that pertinent system variables were used. These variables may include superficial gas velocity, dimensionless aeration numbers for gas systems, and terminal settling velocity for suspensions.

LATEST REVISIONS OF THE APPROACH

As was discussed earlier, the scale-of-agitation approach has been successfully used in scale-up of various liquid systems, including parenteral drugs. However, in the late 1990s, it was slightly revised to assure even more accurate results (7). We have already determined that the mixing in the agitated tank must be in the turbulent state in order for Equation (12) to work properly. Therefore, an assumption is made that full turbulence is achieved at N_{Re} above 2000. However, one should be aware that this assumption may result in an error of 12% in N_Q calculation. One may come to the conclusion that some inadequacies may be encountered in the areas of mixing close to $N_{Re} = 2000$. This later revision of the approach thrived on the fact that because this scale-up process was based on the use of existing equipment, it may not be possible to build in as many safety factors as possible when engineering a new facility. Therefore, it would be important to determine N_Q very accurately. Trying to achieve an even more accurate N_Q determination, the relationship between D/T ratio on the N_{Re} versus N_Q grid was reexamined.

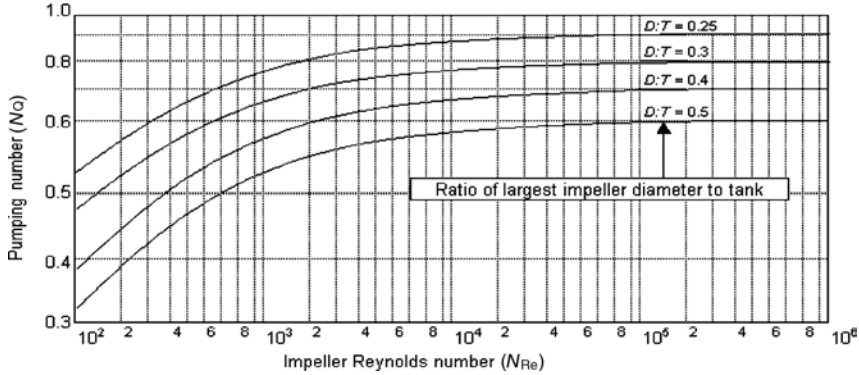

Figure 1 Pumping number versus impeller Reynolds number for turbine and marine type propeller agitators.

Upon replotting Figure 1 using linear coordinates, the following trend was observed (Fig. 2). The curves rise sharply at first, which somewhat resembles dissolution profile for a solid dosage form.

The Lagenbucher's equation for a dissolution profile curves is:

$$Y = 1 - \exp\left[\frac{-(X)^a}{b}\right] \tag{25}$$

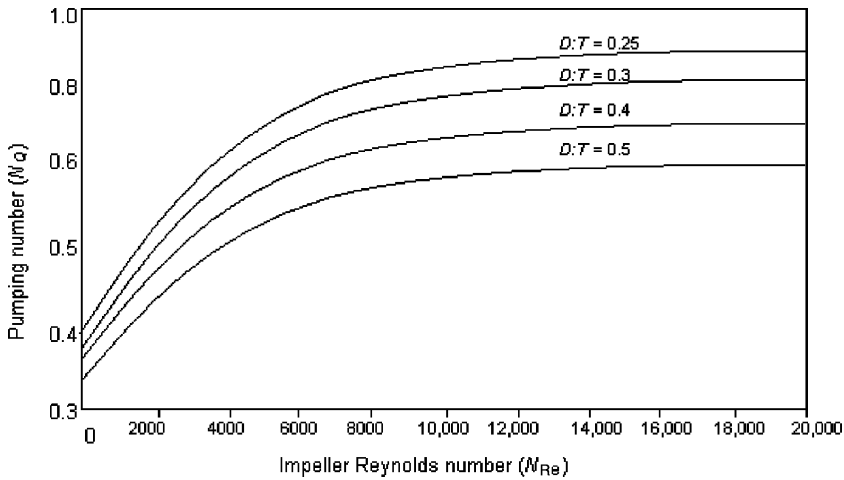

Figure 2 Pumping number versus impeller Reynolds number for turbine and marine type propeller agitators on linear coordinates.

Similarly, an equation for curves in Figure 2 may be expressed as follows where a and b are the constants.

$$N_Q = 1 - \exp\left[\frac{-(N_{Re})^a}{b}\right] \tag{26}$$

Further, the equation for constant a was determined by

$$a = -0.272\left(\frac{D}{T}\right) + 0.39 \tag{27}$$

The constant b was found to be independent of the D/T ratio and had a value of 7.7.

However, Equation (26) only covered applications where N_{Re} is below 1000. Another Equation (20) (8) to determine N_Q in the systems, where N_{Re} is higher than 1000 is

$$N_Q = \frac{AN_{Re}}{N_{Re} + B} \tag{28}$$

where both A and B are the functions of the D/T ratio and where determined to be

$$A = -1.08\left(\frac{D}{T}\right) + 1.12 \tag{29}$$

and

$$B = 578 - 1912\left(\frac{D}{T}\right) + 1980\left(\frac{D}{T}\right)^2 \tag{30}$$

These equations yield an approximate 5% maximum error, as compared to an approximate 10% error in Equation (13).

However, it is also necessary to mention that the strength of the analysis is in its ability to mathematically transfer mixing environment from the bench scale to the maximum compounding vessel, as close to the original pilot batch as possible. In our experience, the maximum rpm ranges empirically achieved during compounding equal 6–20 rpm, which are well within the maximum 10% error that one may encountered by usage of Equation (13) in the marginal cases, where N_{Re} is close to 2000. Therefore, it is safe to conclude that the method outlined in Equations 13–16 is the most efficient to find mixing parameters of the scaled-up system. Yet, Equations 26 and 28 show the way of

closer N_Q determination, which may be more useful for the systems with higher viscosities, thus lower N_{Re}.

SCALE-OF-AGITATION APPROACH FOR SUSPENSIONS

In order to reduce the problem of adequately dispersing the insoluble drug during formulation of sterile aqueous suspensions, micronized material, i.e., material with a particle size of 10–30 μm, is used. Uniform distribution of the drug is required to ensure an adequate dose at the concentration per unit volume indicated on the label. Improper formulation or scale-up can result in caking of the insoluble material at the bottom of the container, making it difficult to disperse, to take up in a syringe, and thus to administer. To avoid caking, various flocculating agents are added to the product. Proper scale-up, however, is essential for adequate mixing conditions, which affect caking process. During scale-up of a suspension product, along with parameters already discussed above, the settling rate should be considered. The presence of a two-phase solid–liquid system classifies an agitation problem as a solid-suspension one. In such problems, the suspension of solid particles having a settling velocity greater than 0.5 ft/min (0.25 cm/sec) within a continuous liquid phase is the purpose of the proper agitation and scale-up. The estimated terminal settling velocity, u_t, of spherical particles of a 10–30 μ size in low viscosity 1–300 cps suspensions, is empirically determined as 1. For ease of analysis, the particle shape is assumed to be a sphere since most of the studies for settling velocities are conducted on spherical beads. The different particle geometry (cylinders, disks, crushed solids, and many crystalline forms) would not compromise the integrity of the analysis due to the usage of micronized materials. First, one must determine design settling velocity u_d, which is

Table 4

Solids (%)	Factor (f_w)
2	0.8
5	0.84
10	0.91
15	1.0
20	1.10
25	1.20
30	1.30
35	1.42
40	1.55
45	1.70
50	1.85

a product of terminal settling velocity, $u_{t,}$ and a correction factor, f_w, from Table 4:

$$u_d = u_t f_w \tag{31}$$

Upon determination of design settling velocity, one must choose the scale of agitation required using Table 5 (9), which serves as the suspension products equivalent of Table 3.

Table 5 Process Requirements Set Degree of Agitation for Solids Suspension

Scale of agitation	Description of mixing
1–2	Agitation levels 1 and 2 are characteristic of applications requiring minimal solids-suspension levels to achieve the process result. Agitators capable of scale levels of 1 will: Produce motion of all of the solids of the design settling velocity in the vessel; Permit moving fillets of solids on the tank bottom, which are periodically suspended.
3–5	Agitation levels 3 and 5 characterize most chemical process industries' solids-suspension applications and are typically used for dissolving solids. Agitators capable of scale levels of 3 will: Suspend all the solids of design settling velocity completely off the vessel bottom; Provide slurry uniformity to at least 1/3 of fluid-batch height; Be suitable for slurry draw-off at low exit-nozzle elevations.
6–8	Agitation levels 6 and 8 characterize applications where the solids-suspension levels approach uniformity. Agitators capable of scale levels of 6 will: Provide concentration uniformity of solids to 95% of the fluid-batch height; Be suitable for slurry draw-off up to 80% of fluid-batch height.
9–10	Agitation levels 9 and 2 characterize applications where the solid-suspension uniformity is the maximum practical. Agitators capable of scale levels of 9 will: Provide slurry uniformity of solids to 98% of the fluid-batch height; Be suitable for slurry draw-off by means of overflow.

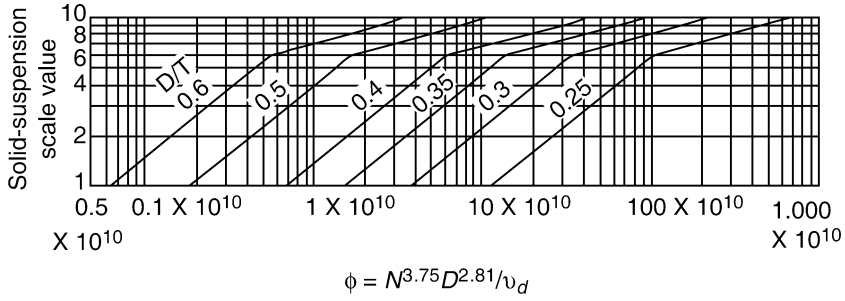

Figure 3 Solid-suspension scale value versus ϕ.

Chosen scale of agitation is then plugged into the Figure 3 chart to find the value of constant ϕ.

Re-arranging Equation (32) for constant ϕ

$$\phi = \frac{N^{3.75} D^{2.81}}{u_{\mathrm{d}}} \tag{32}$$

into Equation (33) for mixer speed, we easily find agitation rpm:

$$N = \frac{1}{3.75} \sqrt{\frac{\phi u_{\mathrm{d}}}{D^{2.81}}} \tag{33}$$

HEAT TRANSFER SCALE-UP CONSIDERATIONS

It is important to add heat transfer scale-up considerations to the scale-up approach for liquid parenteral solutions as heat transfer applications may play a considerable role in preparation of these products. For heat transfer applications, constant horsepower per unit volume is used to achieve approximately similar heat transfer coefficients for the same type of impeller. This approach is a close approximation since the effect of horsepower on the heat transfer coefficient (h_0) is relatively small:

$$h_0 = hp^{0.22} \tag{34}$$

Therefore, even a moderate error in the mixer scale-up will have only a small effect on the agitator-side heat transfer coefficient. Other factors that include heat transfer area per unit volume are considerably more significant. For instance, in the jacketed tank, the heat transfer area per unit volume decreases upon scale-up. In order to assure the same proportionate heat removal or addition per unit batch size, additional heat transfer area (e.g., coils) may be required. Additionally, other variables such as temperature driving force may have to be adjusted to compensate for decreased heat

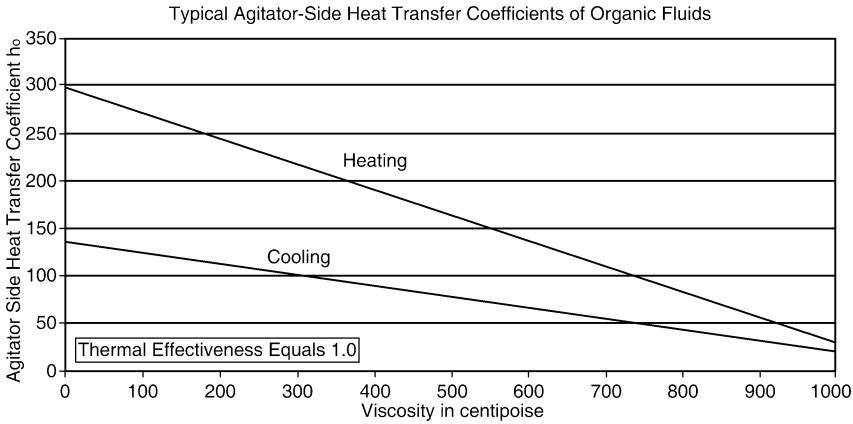

Figure 4 Typical agitator-side heat transfer coefficients of organic fluids.

transfer area. As an aid in preliminary approximation of agitator-side heat transfer coefficients, Figure 4 may be utilized.

Figure 4 shows typical agitator side film coefficients for cooling or heating of organic fluids that serve to provide an "order-of-magnitude" estimate of the agitator-side heat transfer coefficient to embark on preliminary scale-up design work. The heat transfer coefficient will change depending on the specific physical characteristics of the system and the exact agitator selection. The numbers have been generated for the case of the vertical cylinder tubes or a single bank of helical coils. For properly baffled jacketed tanks, approximately 65% decrease of the values shown in Figure 4 may be expected. For inorganic aqueous solutions, the values of heat transfer coefficient shown in Figure 4 may be expected to increase three or four times.

CONCLUSIONS

The above scale-up approach for liquid parenteral solutions provides a precise transfer of the compounding mixing equipment environment to the production scale. Due to the unsurpassed importance of proper agitation during preparation of injectables, the lion's share of this chapter is devoted to scale-up of agitating equipment. Other pieces of equipment used during manufacturing of parenteral drugs, such as sterilization equipment, filtration systems, various pumps and packaging equipment are geometrically scaleable and are easily selected from the wide variety of those available on the market.

One must also stress the importance of quality considerations during compounding and full adherence to current good manufacturing practices while producing parenteral products. Personnel responsible for the process design and scale-up of the equipment must assure proper documentation

of the scale-up with tractability of all the preparatory work from the pilot batch(es) to manufacturing of the marketed products. One can recommend usage of spreadsheet programs for documenting equipment parameters and subsequent calculations required for proper scale-up.

In light of scale-up and postapproval changes (SUPAC) Guidance to the Industry, possible ramifications of the scale-up approach described in this chapter must be considered, as possibilities of interchanging from lower energy to higher energy agitation and vice versa are evident. SUPAC guidance should be followed for appropriate body of evidence to be gathered including sufficient stability studies and appropriate submissions to the agency to be prepared.

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4

Non-Parenteral Liquids and Semisolids

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INTRODUCTION

A manufacturer's decision to scale-up (or scale-down) a process is ultimately rooted in the economics of the production process, i.e., in the cost of material, personnel, and equipment associated with the process and its control. While process scale-up often reduces the unit cost of production and is therefore economically advantageous per se, there are additional economic advantages conferred on the manufacturer by scaling-up a process. Thus, process scale-up may allow for faster entry of a manufacturer into the marketplace or improved product distribution or response to market demands and correspondingly greater market-share retention.[a] Given the potential advantages of process scale-up in the pharmaceutical industry, one would expect the scale-up task to be the focus of major efforts on the part of pharmaceutical manufacturers. However, the paucity of published studies or data on scale-up—particularly for non-parenteral liquids and semisolids—suggests otherwise. On the other hand, one could argue that the paucity of published studies or data is nothing

[a] On the other hand, the manufacturer may determine that the advantages of process scale-up are compromised by the increased cost of production on a larger scale and/or the potential loss of interest or investment income. Griskey (1) addresses the economics of scale-up in some detail in his chapter on engineering economics and process design, but his examples are taken from the chemical industry. For a more extensive discussion of process economics, see Ref. 2.

more than a reflection of the need to maintain a competitive advantage through secrecy.

One could also argue that this deficiency in the literature attests to the complexity of the unit operations involved in pharmaceutical processing. If pharmaceutical technologists view scale-up as little more than a ratio problem, whereby

$$\text{Scale-up ratio} = \frac{\text{Large-scale production rate}}{\text{Small-scale production rate}} \quad (1)$$

then the successful resolution of a scale-up problem will remain an empirical, trial-and-error task rather than a scientific one. In 1998, in a monograph on the scale-up of disperse systems, Block (3) noted that due to the complexity of the manufacturing process which involves more than one type of unit operation[b] (e.g., mixing, transferring, etc.), process scale-up from the bench or pilot plant level to commercial production is not a simple extrapolation:

> "The successful linkage of one unit operation to another defines the functionality of the overall manufacturing process. Each unit operation per se may be scalable, in accordance with a specific ratio, but the composite manufacturing process may not be, as the effective scale-up ratios may be different from one unit operation to another. Unexpected problems in scale-up are often a reflection of the dichotomy between *unit operation* scale-up and *process* scale-up. Furthermore, commercial production introduces problems that are not a major issue on a small scale: e.g., storage and materials handling may become problematic only when large quantities are involved; heat generated in the course of pilot plant or production scale processing may overwhelm the system's capacity for dissipation to an extent not anticipated based on prior laboratory-scale experience (3)."

Furthermore, unit operations may function in a rate-limiting manner as the scale of operation increases. When Astarita (4) decried the fact, in the mid-1980s, that "there is no scale-up algorithm which permits us to rigorously predict the behavior of a large scale process based upon the behavior of a small scale process," it was presumably as a consequence of all of these problematic aspects of scale-up.

A clue to the resolution of the scale-up problem for liquids and semisolids resides in the recognition that their processing invariably involves the

[b] The term *unit operations*, coined by Arthur D. Little in 1915, is generally used to refer to distinct *physical* changes or unit actions (e.g., pulverizing, mixing, drying, etc.) while unit operations involving *chemical* changes are sometimes referred to as *unit processes*. The physical changes comprising unit operations primarily involve contact, transfer of a physical property, and separation between phases or streams.

unit operation of mixing. Closer examination of this core unit operation reveals that flow conditions and viscosities during processing can vary by several orders of magnitude depending upon the scale of scrutiny employed, i.e., whether on a *micro*scopic (e.g., μm to cm) or *macro*scopic (e.g., cm to m) scale. The key to effective processing scale-up is the appreciation and understanding of microscale and macroscale transport phenomena, i.e., diffusion and bulk flow, respectively. Transport by diffusion involves the flow of a property (e.g., mass, heat, momentum, and electromagnetic energy) from a region of high concentration to a region of low concentration as a result of the microscopic motion of electrons, atoms, molecules, etc. Bulk flow, whether convection or advection, however, involves the flow of a property as a result of macroscopic or bulk motion induced artificially (e.g., by mechanical agitation) or naturally (e.g., by density variations) (5).

TRANSPORT PHENOMENA IN LIQUIDS AND SEMISOLIDS AND THEIR RELATIONSHIP TO UNIT OPERATIONS AND SCALE-UP

Over the last four decades or so, transport phenomena research has benefited from the substantial efforts made to replace empiricism by fundamental knowledge based on computer simulations and theoretical modeling of transport phenomena. These efforts were spurred on by the publication in 1960 by Bird et al. (6) of the first edition of their quintessential monograph on the interrelationships among the three fundamental types of transport phenomena: mass transport, energy transport, and momentum transport.[c] All transport phenomena follow the same pattern in accordance with the generalized diffusion equation (GDE). The unidimensional *flux*, or overall transport rate per unit area in one direction, is expressed as a system property multiplied by a gradient (5)

$$\left.\frac{\partial \Gamma}{\partial t}\right|_x = \delta\left(\frac{\partial^2 \Gamma}{\partial x^2}\right) = \delta\left(\frac{\left(\frac{\partial \Gamma}{\partial x}\right)}{\partial x}\right) = \delta\left(\frac{\partial E}{\partial x}\right) \tag{2}$$

where Γ represents the concentration of a property Q (e.g., mass, heat, electrical energy, etc.) per unit volume, i.e., $\Gamma = Q/V$, t is time, x is the distance measured in the direction of transport, δ is the generalized diffusion coefficient, and E is the gradient or driving force for transport.

Mass and heat transfer can be described in terms of their respective concentrations Q/V. While the concentration of mass, m, can be specified directly, the concentration of heat is given by

[c] The second edition of *Transport Phenomena* was published in 2002, 42 years later, an indication of the utility of the first edition and its continuing acceptance by the engineering discipline.

$$\frac{mC_pT}{V} = \rho C_pT \tag{3}$$

where C_p is the specific heat capacity and T is temperature. Thus the specification of ρC_pT in any form of the generalized diffusion equation will result in the elimination of ρC_p, assuming it to be a constant, thereby allowing the use of temperature as a measure of heat concentration (5). In an analogous manner, momentum transfer can be specified in terms of the concentration of momentum u when its substantial derivative is used instead of its partial derivative with respect to time

$$\frac{D\mathbf{u}}{Dt} = \nu\nabla^2\mathbf{u} \tag{4}$$

where ν is the kinematic viscosity. If pressure and gravitational effects are introduced, one arrives at the Navier–Stokes relationships that govern Newtonian fluid dynamics.

When the flux of Γ is evaluated three-dimensionally, it can be represented by (5)

$$\frac{d\Gamma}{dt} = \frac{\partial\Gamma}{\partial t} + \frac{\partial\Gamma}{\partial x}\frac{dx}{dt} + \frac{\partial\Gamma}{\partial y}\frac{dy}{dt} + \frac{\partial\Gamma}{\partial z}\frac{dz}{dt} \tag{5}$$

At the simplest level, as Griskey (1) notes, Fick's law of diffusion for mass transfer and Fourier's law of heat conduction characterize mass and heat transfer, respectively, as vectors, i.e., they have magnitude and direction in the three coordinates, x, y, and z. Momentum or flow, however, is a tensor which is defined by nine components rather than three. Hence, its more complex characterization at the simplest level, in accordance with Newton's law, is

$$\tau_{yx} = -\eta\left(\frac{dv_x}{dy}\right) \tag{6}$$

where τ_{yx} is the shear stress in the x-direction, (dv_x/dy) the rate of shear, and η is the coefficient of Newtonian viscosity. The solution of Equation (2), the generalized diffusion equation,

$$\Gamma = f(t, x, y, z) \tag{7}$$

will take the form of a parabolic partial differential equation (5). However, the more complex the phenomenon—e.g., with convective transport a part of the model—the more difficult it is to achieve an analytic solution to the GDE. Numerical solutions, however, where the differential equation is transformed to an algebraic one, may be somewhat more readily achieved.

Transport Phenomena and Their Relationship to Mixing as a Unit Operation[d]

As noted earlier, virtually all liquid and semisolid products involve the unit of operation of mixing.[e] In fact, in many instances, it is the primary unit operation. Even its indirect effects, e.g., on heat transfer, may be the basis for its inclusion in a process. Yet, mechanistic and quantitative descriptions of the mixing process remain incomplete (7–9). Nonetheless, enough fundamental and empirical data are available to allow some reasonable predictions to be made.

The diversity of dynamic mixing devices is unsettling: their dynamic, or moving, component's blades may be impellers in the form of propellers, turbines, paddles, helical ribbons, Z-blades, or screws. In addition, one can vary the number of impellers, the number of blades per impeller, the pitch of the impeller blades, and the location of the impeller, and thereby affect mixer performance to an appreciable extent. Furthermore, while dispersators or rotor/stator configurations may be used rather than impellers to effect mixing, mixing may also be accomplished by jet-mixing or static-mixing devices. The bewildering array of mixing equipment choices alone would appear to make the likelihood of effective scale-up an impossibility. However, as diverse as mixing equipment may be, evaluations of the rate and extent of mixing and of flow regimes[f] make it possible to find a common basis for comparison.

In low-viscosity systems, miscible liquid blending is achieved through the transport of unmixed material via flow currents (i.e., bulk or convective flow) to a mixing zone (i.e., a region of high shear or intensive mixing). In other words, mass transport during mixing depends on *streamline* or *laminar* flow, involving well-defined paths, and *turbulent* flow, involving innumerable, variously sized, eddies, or swirling motions. Most of the highly turbulent mixing takes place in the region of the impeller, fluid motion elsewhere serving primarily to bring fresh fluid into this region. Thus, the characterization of mixing processes is often based on the flow regimes encountered in mixing equipment. Reynolds' classic research on flow in pipes demonstrated

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[d]Reprinted in part, with revisions and updates, by courtesy of Marcel Dekker, Inc., from L. H. Block, "Scale-up of disperse systems: Theoretical and practical aspects," in Pharmaceutical Dosage Forms: Disperse Systems (H. A. Lieberman, M. M. Rieger, and G. S. Banker, eds.), Vol. 3, 2nd ed., New York: Marcel Dekker, 1998:366–378.

[e]*Mixing*, or *blending*, refers to the random distribution of two or more initially separate phases into and through one another, while *agitation* refers only to the induced motion of a material in some sort of container. Agitation does not necessarily result in an intermingling of two or more separate components of a system to form a more or less uniform product. Some authors reserve the term *blending* for the intermingling of miscible phases while *mixing* is employed for materials that may or may not be miscible.

[f]The term *flow regime* is used to characterize the hydraulic conditions (i.e., volume, velocity, and direction of flow) within a vessel.

that flow changes from laminar to irregular, or turbulent, once a critical value of a dimensionless ratio of variables has been exceeded (10,11). This ratio, universally referred to as the Reynolds number, N_{Re}, is defined by Equations (8a) and (8b),

$$N_{Re} = \frac{Lv\rho}{\eta} \tag{8a}$$

$$N_{Re} = \frac{D^2 N\rho}{\eta} \tag{8b}$$

where ρ is the density, v the velocity, L the characteristic length, and η is the Newtonian viscosity; Equation (8b) is referred to as the *impeller* Reynolds number, as D is the impeller diameter and N is the rotational speed of the impeller. N_{Re} represents the ratio of the inertia forces to the viscous forces in a flow. High values of N_{Re} correspond to flow dominated by motion while low values of N_{Re} correspond to flow dominated by viscosity. Thus, the transition from laminar to turbulent flow is governed by the density and viscosity of the fluid, its average velocity, and the dimensions of the region in which flow occurs (e.g., the diameter of the pipe or conduit, the diameter of a settling particle, etc.). For a straight circular pipe, laminar flow occurs when $N_{Re} < 2100$; turbulent flow is evident when $N_{Re} > 4000$. For $2100 \leq N_{Re} \leq 4000$, flow is in transition from a laminar to a turbulent regime. Other factors such as surface roughness, shape and cross-sectional area of the affected region, etc., have a substantial effect on the critical value of N_{Re}. Thus, for particle sedimentation, the critical value of N_{Re} is 1; for some mechanical mixing processes, N_{Re} is 10–20 (12). The erratic, relatively unpredictable nature of turbulent eddy flow is further influenced, in part, by the size distribution of the eddies which are dependent on the size of the apparatus and the amount of energy introduced into the system (10). These factors are indirectly addressed by N_{Re}. Further insight into the nature of N_{Re} can be gained by viewing it as inversely proportional to eddy advection time, i.e., the time required for eddies or vortices to form.

In turbulent flow, eddies move rapidly with an appreciable component of their velocity in the direction perpendicular to a reference point, e.g., a surface past which the fluid is flowing (13). Because of the rapid eddy motion, mass transfer in the turbulent region is much more rapid than that resulting from molecular diffusion in the laminar region, with the result that the concentration gradients existing in the turbulent region will be smaller than those in the laminar region (13). Thus, mixing is much more efficient under turbulent flow conditions. Nonetheless, the technologist should bear in mind potentially compromising aspects of turbulent flow, e.g., increased vortex formation (14) and a concomitant incorporation of air, increased shear and a corresponding shift in the particle size distribution of the disperse phase, etc.

Although continuous-flow mixing operations are employed to a limited extent in the pharmaceutical industry, the processing of liquids and semisolids most often involves batch processing in some kind of tank or vessel. Thus, in the general treatment of mixing that follows, the focus will be on batch operations[g] in which mixing is accomplished primarily by the use of dynamic mechanical mixers with impellers, although jet mixing (17,18) and static mixing devices (19)—long used in the chemical process industries—are being used to an increasingly greater extent now in the pharmaceutical and cosmetic industries.

Mixers share a common functionality with pumps. The power imparted by the mixer, via the impeller, to the system is akin to a pumping effect and is characterized in terms of the shear and flow produced as

$$P \propto Q\rho H$$

or

$$H \propto \frac{P}{Q\rho} \tag{9}$$

where P is the power imparted by the impeller, Q the flow rate (or pumping capacity) of material through the mixing device, ρ the density of the material, and H is the velocity head or shear. Thus, for a given P, there is an inverse relationship between shear and volume throughput.

The power input in mechanical agitation is calculated using the *power number*, N_P,

$$N_P = \frac{Pg_c}{\rho N^3 D^5} \tag{10}$$

where g_c is the force conversion factor $\left(g_c = \frac{\text{kg} \bullet \text{m} \bullet \text{sec}^{-2}}{\text{N}} = \frac{\text{g} \bullet \text{cm} \bullet \text{sec}^{-2}}{\text{dyne}}\right)$, N the impeller rotational speed (sec^{-1}), and D is the diameter of the impeller. For a given impeller/mixing tank configuration, one can define a specific relationship between the Reynolds number [Eq. (8)][h] and the power number [Eq. (10)] in which three zones (corresponding to the laminar, transitional, and turbulent regimes) are generally discernible. Tatterson (20) notes that for mechanical agitation in laminar flow, most *laminar* power correlations reduce to $N_p N_{Re} = B$, where B is a complex function of the geometry of the system,[i] and that this is equivalent to $P \propto \eta \cdot h \cdot N^2 D^3$; "if power correlations do not reduce to this form

[g] The reader interested in continuous-flow mixing operations is directed to references that deal specifically with that aspect of mixing such as the monographs by Oldshue (15) and Tatterson (16).

[h] Here, the Reynolds number for mixing is defined in SI-derived units as $N_{Re} = (1.667 \times 10^{-5} N D^2 \rho)/\eta$, where D, impeller diameter, is in mm.; η is in Pa•s; N is impeller speed, in r.p.m.; and ρ is density.

[i] An average value of B is 300, but B can vary between 20 and 4000 (20).

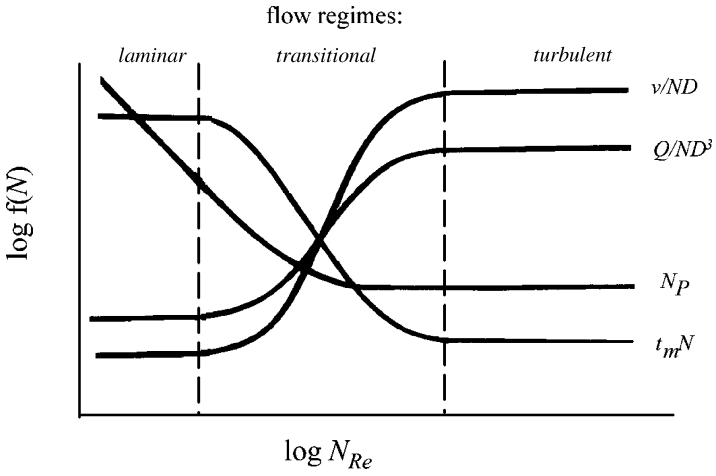

Figure 1 Various dimensionless parameters [dimensionless velocity, $v^* = v/ND$; pumping number, $N_Q = Q/ND^3$; power number, $N_P = \left(Pg_c/\rho N^3 D^5\right)$; and dimensionless mixing time, $t^* = t_m N$] as a function of the Reynolds number for the analysis of turbine–agitator systems. *Source*: Adapted from Ref. 22.

for laminar mixing, then they are wrong and should not be used." Turbulent correlations are much simpler: for systems employing baffles,[j] $N_P = B$; this is equivalent to $P \propto \rho N^3 D^5$. Based on this function, slight changes in D can result in substantial changes in power.

Impeller size relative to the size of the tank is critical as well. If the ratio of impeller diameter D to tank diameter T is too large (D/T is $> \sim 0.7$), mixing efficiency will decrease as the space between the impeller and the tank wall will be too small to allow a strong axial flow due to obstruction of the recirculation path (21). More intense mixing at this point would require an increase in impeller speed, but this may be compromised by limitations imposed by impeller blade thickness and angle. If D/T is too small, the impeller will not be able to generate an adequate flow rate in the tank.

Valuable insights into the mixing operation can be gained from a consideration of system behavior as a function of the Reynolds number, N_{Re} (22). This is shown schematically in Figure 1 in which various dimensionless parameters (dimensionless velocity, v/ND; pumping number, Q/ND^3; power number, $N_P = \left(Pg_c/\rho N^3\ D^5\right)$; and dimensionless mixing time, $t_m N$) are represented as a log–log function of N_{Re}. Although density, viscosity, mixing vessel diameter, and impeller rotational speed are often viewed by

[j] Baffles are obstructions placed in mixing tanks to redirect flow and minimize vortex formation. Standard baffles—comprising rectangular plates spaced uniformly around the inside wall of a tank—convert rotational flow into top-to-bottom circulation.

formulators as independent variables, their interdependency, when incorporated in the dimensionless Reynolds number, is quite evident. Thus, the schematic relationships embodied in Figure 1 are not surprising.[k]

Mixing time is the time required to produce a mixture of predetermined quality; the rate of mixing is the rate at which mixing proceeds towards the final state. For a given formulation and equipment configuration, mixing time, t_m, will depend upon material properties and operation variables. For geometrically similar systems, if the geometrical dimensions of the system are transformed to ratios, mixing time can be expressed in terms of a dimensionless number, i.e., the dimensionless mixing time, θ_m or $t_m N$

$$t_m N = \theta_m = f(N_{Re}, N_{Fr}) \Longrightarrow f(N_{Re}) \tag{11}$$

The Froude number, $N_{Fr} = (\nu/\sqrt{Lg})$, is similar to N_{Re}; it is a measure of the inertial stress to the gravitational force per unit area acting on a fluid. Its inclusion in Equation (11) is justified when density differences are encountered; in the absence of substantive differences in density, e.g., for emulsions more so than for suspensions, the Froude term can be neglected. Dimensionless mixing time is independent of the Reynolds number for both laminar and turbulent flow regimes as indicated by the plateaus in Figure 1. Nonetheless, as there are conflicting data in the literature regarding the sensitivity of θ_m to the rheological properties of the formulation and to equipment geometry, Equation (11) must be regarded as an oversimplification of the mixing operation. Considerable care must be exercised in applying the general relationship to specific situations.

Empirical correlations for *turbulent* mechanical mixing have been reported in terms of the following dimensionless mixing time relationship (24)

$$\theta_m = t_m N = K\left(\frac{T}{D}\right)^a \tag{12}$$

where K and a are constants, T is tank diameter, N is impeller rotational speed, and D is the impeller diameter. Under *laminar* flow conditions, Equation (12) reduces to

$$\theta_m = H_0 \tag{13}$$

where H_0 is referred to as the mixing number or homogenization number. In the *transitional* flow regime,

$$H_0 = C(N_{Re})^a \tag{14}$$

where C and a are constants, with a varying between 0 and -1.

[k] The interrelationships are embodied in variations of the Navier–Stokes equations, which describe mass and momentum balances in fluid systems (23).

Flow patterns in agitated vessels may be characterized as radial, axial, or tangential relative to the impeller, but are more correctly defined by the direction and magnitude of the velocity vectors throughout the system, particularly in a transitional flow regime; while the dimensionless velocity, ν^*, or ν/ND, is essentially constant in the laminar and turbulent flow zones, it is highly dependent on N_{Re} in the transitional flow zone (Fig. 1). Initiation of tangential or circular flow patterns with minimal radial or axial movement is associated with vortex formation, minimal mixing, and, in some multiphase systems, particulate separation and classification. Vortices can be minimized or eliminated altogether by redirecting flow in the system through the use of baffles[1] or by positioning the impeller so that its entry into the mixing tank is off-center. For a given formulation, large tanks are more apt to exhibit vortex formation than small tanks. Thus, full scale production tanks are more likely to require baffles even when smaller (laboratory or pilot plant scale) tanks are unbaffled.

Mixing processes involved in the manufacture of disperse systems, whether suspensions or emulsions, are far more problematic than those employed in the blending of low-viscosity miscible liquids due to the multiphasic character of the systems and deviations from Newtonian flow behavior. It is not uncommon for both laminar and turbulent flow to occur simultaneously in different regions of the system. In some regions, the flow regime may be in transition, i.e., neither laminar nor turbulent but somewhere in between. The implications of these flow regime variations for scale-up are considerable. Nonetheless, it should be noted that the mixing process is only completed when Brownian motion occurs sufficiently to achieve uniformity on a molecular scale.

Viscous and Non-Newtonian Materials

Mixing in high-viscosity materials ($\eta > \sim 10^4$ cPs) is relatively slow and inefficient. Conventional mixing tanks and conventional impellers (e.g., turbine or propellor impellers) are generally inadequate. In general, due to the high viscosity, N_{Re} may well be below 100. Thus, laminar flow is apt to occur rather than turbulent flow. As a result, the inertial forces imparted to a system during the mixing process tend to dissipate quickly. Eddy formation and diffusion are virtually absent. Thus, efficient mixing necessitates substantial convective flow which is usually achieved by high-velocity gradients in the mixing zone. Fluid elements in the mixing zone, subjected to both shear and elongation, undergo deformation and stretching, ultimately resulting in the size reduction of the fluid elements and an increase in their overall interfacial area. The repetitive

[1]The usefulness of baffles in mixing operations is offset by increased clean-up problems (due to particulate entrapment by the baffles or congealing of product adjacent to the baffles). Furthermore, "overbaffling"—excessive use of baffles—reduces mass flow and localizes mixing, which may be counterproductive.

cutting and folding of fluid elements also result in decreasing inhomogeneity and increased mixing. The role of molecular diffusion in reducing inhomogeneities in high-viscosity systems is relatively unimportant until these fluid elements have become small and their interfacial areas have become relatively large (25). In highly viscous systems, rotary motion is more than compensated for by viscous shear so that baffles are generally less necessary (26).

Mixing equipment for highly viscous materials often involves specialized impellers and configurations which minimize high-shear zones and heat dissipation. Accordingly, propeller-type impellers are not generally effective in viscous systems. Instead, turbines, paddles, anchors, helical ribbons, screws, and kneading mixers are resorted to, successively, as system viscosity increases. Multiple impellers or specialized impellers (e.g., sigma-blades, Z-blades, etc.) are often necessary, along with the maintenance of narrow clearances or gaps between impeller blades and between impeller blades and tank (mixing chamber) walls in order to attain optimal mixing efficiency (25,26). However, narrow clearances pose their own problems. Studies of the power input to anchor impellers used to agitate Newtonian and shear-thinning fluids showed that the clearance between the impeller blades and the vessel wall was the most important geometrical factor; N_P at constant N_{Re} was proportional to the fourth power of the clearance divided by tank diameter (27). Furthermore, although mixing is promoted by these specialized impellers in the vicinity of the walls of the mixing vessel, stagnation is often encountered in regions adjacent to the impeller shaft. Finally, complications (wall effects) may arise from the formation of a thin, particulate-free, fluid layer adjacent to the wall of the tank or vessel that has a lower viscosity than the bulk material and allows slippage (i.e., non-zero velocity) to occur, unless the mixing tank is further modified to provide for wall-scraping.

Rheologically, the flow of many non-Newtonian materials can be characterized by a time-independent power law function (sometimes referred to as the Ostwald-deWaele equation)

$$\tau = K\dot{\gamma}^a$$

or

$$\log \tau = K' + a(\log \dot{\gamma}) \tag{15}$$

where τ is the shear stress, $\dot{\gamma}$ the rate of shear, K' the logarithmically transformed proportionality constant K with dimensions dependent upon a, the so-called flow behavior index. For pseudoplastic or shear-thinning materials, $a < 1$; for dilatant or shear-thickening materials, $a > 1$; for Newtonian fluids, $a = 1$. For a power-law fluid, the average apparent viscosity, η_{avg}, can be related to the average shear rate by the following equation:

$$\eta_{avg} = K' \left(\frac{d\nu}{dy} \right)_{avg}^{n'-1} \tag{16}$$

Based on this relationship, a Reynolds number can be derived and estimated for non-Newtonian fluids from:

$$\left[N_{\mathrm{Re}} = \frac{L\nu\rho}{\eta}\right] \Longrightarrow \left[N_{\mathrm{Re,nonN}} = \frac{ND_i^2\rho}{K'(\mathrm{d}\nu/\mathrm{d}y)_{\mathrm{avg}}^{n'-1}}\right] \tag{17}$$

Dispersions that behave, rheologically, as Bingham plastics require a minimum shear stress (the yield value) in order for flow to occur. Shear stress variations in a system can result in local differences wherein the yield stress point is not exceeded. As a result, flow may be impeded or absent in some regions compared to others, resulting in channeling or cavity formation and a loss of mixing efficiency. Only if the yield value is exceeded *throughout* the system will flow and mixing be relatively unimpeded. Helical ribbon and screw impellers would be preferable for the mixing of Bingham fluids, in contrast to conventional propeller or turbine impellers, given their more even distribution of power input (28). From a practical vantage point, monitoring power input to mixing units could facilitate process control and help to identify problematic behavior. Etchells et al. (29) analyzed the performance of industrial mixer configurations for Bingham plastics. Their studies indicate that the logical scale-up path from laboratory to pilot plant to production, for geometrically similar equipment, involves the maintenance of constant impeller tip speed which is proportional to $N \bullet D$, the product of rotational speed of the impeller (N) and the diameter of the impeller (D).

Oldshue (26) provides a detailed procedure for selecting mixing times and optimizing mixer and impeller configurations for viscous and shear-thinning materials, which can be adapted for other rheologically challenging systems.

Gate and anchor impellers, long used advantageously for the mixing of viscous and non-Newtonian fluids, induce complex flow patterns in mixing tanks; both primary and secondary flows may be evident. *Primary* flow or circulation results from the direct rotational movement of the impeller blade in the fluid; *secondary* flow is normal to the horizontal planes about the impeller axis (i.e., parallel to the impeller axis) and is responsible for the interchange of material between different levels of the tank (31). In this context, rotating viscoelastic systems, with their normal forces, establish stable secondary flow patterns more readily than Newtonian systems. In fact, the presence of normal stresses in viscoelastic fluids subjected to high rates of shear ($\sim 10^4$/sec) may be substantially greater than shearing stresses, as demonstrated by Metzner et al. (31). These observations, among others, moved Fredrickson (32) to note that "... neglect of normal stress effects is likely to lead to large errors in theoretical calculations for flow in complex geometries." However, the effect of these secondary flows on the efficiency of mixing, particularly in viscoelastic systems, is equivocal. On the one hand,

vertical velocity near the impeller blade in a Newtonian system might be 2–5% of the horizontal velocity, whereas in a non-Newtonian system, vertical velocity can be 20–40% of the horizontal. Thus, the overall circulation can improve considerably. On the other hand, the relatively small, stable, toroidal vortices that tend to form in viscoelastic systems may result in substantially incomplete mixing. Smith (30) advocates the asymmetric placement of small deflector blades on a standard anchor arm as a means of achieving dramatic improvement in mixing efficiency of viscoelastic fluids without resorting to expensive alternatives such as pitched blade anchors or helical ribbons.

Sidewall clearance, i.e., the gap between the vessel wall and the rotating impeller, was shown by Cheng et al. (33) to be a significant factor in the mixing performance of helical ribbon mixers not only for viscous and viscoelastic fluids, but also for Newtonian systems. Bottom clearance, i.e., the space between the base of the impeller and the bottom of the tank, however, had a negligible, relatively insignificant effect on power consumption and on the effective shear rate in inelastic fluids. Thus, mixing efficiency in non-viscoelastic fluids would not be affected by variations in bottom clearance. On the other hand, bottom clearance effects were negligible only at lower rotational speeds ($\leq$60 rpm) for viscoelastic fluids; substantial power consumption increases were evident at higher rotational speeds.

The scale-up implications of *mixing*-related issues such as impeller design and placement, mixing tank characteristics, new equipment design, the mixing of particulate solids, etc., are beyond the scope of this chapter. However, extensive monographs are available in the chemical engineering literature (many of which have been cited herein[m]) and will prove to be invaluable to the formulator and technologist.

Particle Size Reduction

Disperse systems often necessitate particle size reduction, whether it is an integral part of product processing, as in the process of liquid–liquid emulsification, or an additional requirement insofar as solid particle suspensions are concerned. (It should be noted that solid particles suspended in liquids often tend to agglomerate. Although milling of such suspensions tends to disrupt such agglomerates and produce a more homogeneous suspension,

[m] The reader is directed to previously referenced monographs by Oldshue and by Tatterson as well as to standard textbooks in chemical engineering, including the multivolume series authored by McCabe et al., and the encyclopedic *Perry's Chemical Engineers' Handbook*. An excellent resource is the *Handbook of Industrial Mixing*: *Science and Practice*, edited by E. L. Paul, V. A. Atiemo-Obeng, and S. M. Kresta, and published in 2004.

it generally does not affect the size of the unit particles comprising the agglomerates.) For emulsions, the dispersion of one liquid as droplets in another can be expressed in terms of the dimensionless Weber number, N_{We}

$$N_{We} = \frac{\rho \nu^2 d_0}{\sigma} \tag{18}$$

where ρ is the density of a droplet, ν is the relative velocity of the moving droplet, d_0 is the diameter of the droplet, and σ is the interfacial tension. The Weber number represents the ratio of the driving force causing partial disruption to the resistance due to interfacial tension (34). Increased Weber numbers are associated with a greater tendency for droplet deformation (and consequent splitting into still smaller droplets) to occur at higher shear, i.e., with more intense mixing. This can be represented by

$$N_{We} = \frac{D_i^3 N^2 \rho_{cont}}{\sigma} \tag{19}$$

where D_i is the diameter of the impeller, N is the rotational speed of the impeller, and ρ_{cont} is the density of the continuous phase. For a given system, droplet size reduction begins above a specific critical Weber number (35); above the critical N_{We}, average droplet size varies with $N^{-1.2} D_i^{-0.8}$, or, as an approximation, with the reciprocal of the impeller tip speed. In addition, a better dispersion is achieved with a smaller impeller rotating at high speed for the same power input (36).

As the particle size of the disperse phase decreases, there is a corresponding increase in the number of particles and a concomitant increase in interparticulate and interfacial interactions. Thus, in general, the viscosity of a dispersion is greater than that of the dispersion medium. This is often characterized in accordance with the classical Einstein equation for the viscosity of a dispersion,

$$\eta = \eta_0(1 + 2.5\phi) \tag{20}$$

where η is the viscosity of the dispersion, η_0 is the viscosity of the continuous phase, and ϕ is the volume fraction of the particulate phase. The rheological behavior of concentrated dispersions may be demonstrably non-Newtonian (pseudoplastic, plastic, or viscoelastic) and its dependence on ϕ more marked due to disperse phase deformation and/or interparticulate interaction.

Maa and Hsu (37) investigated the influence of operation parameters for rotor/stator homogenization on emulsion droplet size and temporal stability in order to optimize operating conditions for small- and large-scale rotor/stator homogenization. Rotor/stator homogenization effects emulsion formation under much more intense turbulence and shear than that encountered in an agitated vessel or a static mixer. Rapid circulation, high shear forces, and a narrow rotor/stator gap (<0.5 mm) contribute to the intensity of dispersal and commingling of the immiscible phases since

turbulent eddies are essential for the breakup of the dispersed phase into droplets. Maa and Hsu's estimates of the circulation rates in small- and large-scale rotor/stator systems—based on the total area of the rotor/stator openings, the radial velocity at the openings (resulting from the pressure difference within the vortex that forms in the rotor/stator unit), and the centrifugal force caused by the radial deflection of fluid by the rotor—appear to be predictive for the scale-up of rotor/stator homogenization (37).

Dobetti and Pantaleo (38) investigated the influence of hydrodynamic parameters per se on the efficiency of a coacervation process for microcapsule formation. They based their work on that of Armenante and Kirwan (39) who described the size of the smallest eddies or vortices generated in a turbulent regime on a microscopic scale in the vicinity of the agitation source, i.e., microeddies,[n] as

$$d_e = \left(\frac{\nu^3}{P_s}\right)^{1/4} \tag{21}$$

where d_e is the diameter of the smallest microeddy, v is the kinematic viscosity of the fluid (i.e., η/ρ, or viscosity/density), and P_s is the specific power, i.e., power input per unit mass. Hypothetically, if mass transfer of the coacervate and particle encapsulation occurred only within the microeddies, then the diameter of the hardened microcapsules would depend on the size of the microeddies produced by the agitation in the system. They dispersed a water-insoluble drug in a cellulose acetate phthalate (CAP) solution to which a coacervation-inducing agent was gradually added to facilitate microencapsulation by the CAP coacervate phase. The stirring rate and the tank and impeller configuration were varied to produce an array of microeddy sizes. However, the actual size of the hardened microcapsules was less than that calculated for the corresponding microeddies (Fig. 2). The authors attributed the inequality in sizes, in part, to relatively low agitation energies. Their conclusion is supported by their calculated N_{Re} values, ranging from 1184 to 2883, which are indicative of a flow regime ranging from laminar to transitional, rather than turbulent.

Comminution, or particle size reduction of solids, is considerably different from that of the breakup of one liquid by dispersal as small droplets in another. Particle size reduction is generally achieved by one of four mechanisms: (1) compression, (2) impact, (3) attrition and (4) cutting or shear. Equipment for particle size reduction or milling includes *crushers* (which operate by compression, e.g., crushing rolls), *grinders* (which operate principally by impact and attrition, although some compression may be involved, e.g.,

[n] Deduced in 1941 by A. N. Kolmogorov, it is generally referred to the Kolmogorov length or dissipation scale (9).

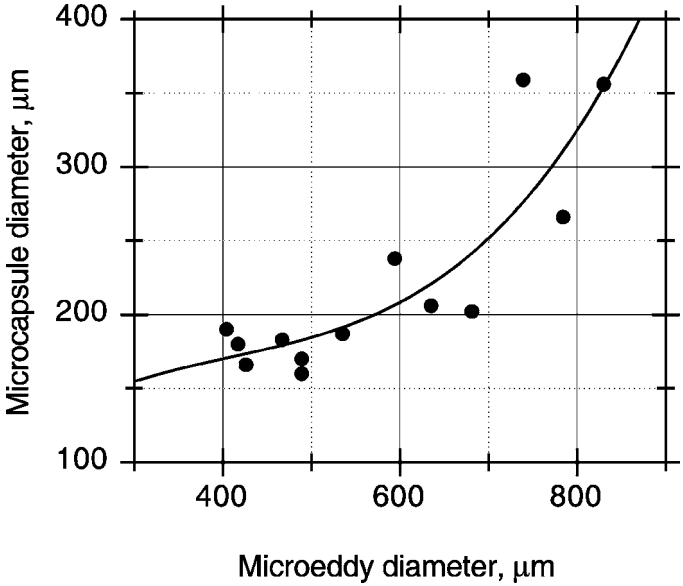

Figure 2 Microcapsule size as a function of microeddy size. *Source*: Adapted from Ref. 37.

hammer mills and ball mills), *ultrafine grinders* (which operate principally by attrition, e.g., fluid-energy mills), and *knife cutters*. Accordingly, a thorough understanding of milling operations requires an understanding of fracture mechanics, agglomerative forces (dry and wet) involved in the adhesion and cohesion of particulates, and flow of particles and bulk powders. These topics are dealt with at length in the monographs by Fayed and Otten (40) and Carstensen (41,42).

As Austin (43) notes, the formulation of a general theory of the unit operation of size reduction is virtually impossible given the multiplicity of mill types and mechanisms for particulate reduction. The predictability of any comminution process is further impaired given the variations among solids in surface characteristics and reactivity, molecular interactions, crystallinity, etc. Nonetheless, some commonalities can be discerned. First, the particle size reduction rate is dependent upon particle strength and particle size. Second, the residence time of particles in the mill is a critical determinant of mill efficiency. Thus, whether a given mill operates in a single pass or a multiple pass (retention) mode can be a limiting factor insofar as characterization of the efficacy of comminution is concerned. Third, the energy required to achieve a given degree of comminution is an inverse function of initial particle size. This is due to (1) the increasing inefficiency of stress or shear application to each particle of an array of particles as particle size

decreases and (2) the decreasing incidence of particle flaws which permit fracture at low stress (43).

If monosized particles are subjected to one pass through a milling device, the particle size distribution of the resultant fragments can be represented in a cumulative form. Subsequent passes of the comminuted material through the milling device often result in a superimposable frequency distribution when the particle sizes are normalized, e.g., in terms of the weight fraction less than size y resulting from the milling of particles of larger size x. The mean residence time, τ, of material processed by a mill is given by

$$\tau = \frac{M}{F} \tag{22}$$

where M is the mass of powder in the mill and F is the mass flow rate through the mill. Process outcomes for retention mills can be described in terms of residence time distributions defined by the weight fraction of the initial charge at time $t = 0$, which leaves between $(t + \mathrm{d}t)$. If the milling operation is scalable, the particle size distributions produced by a large and a small mill of the same type would be comparable and would differ only in the time scale of operation, i.e., the operation can be characterized as a $f(t/\tau)$. The prospect for scalability may be further enhanced when the weight fraction remaining in an upper range is a log-linear (first order) function of total elapsed milling time (42).[o] Corroboration of the likelihood of scalability of milling operations is Mori's finding that most residence time distributions for milling conform to a log-normal model (44).

One estimate of the efficacy of a crushing or grinding operation is the crushing efficiency, E_c, described as the ratio of the surface energy created by crushing or grinding to the energy absorbed by the solid (45).

$$E_c = \frac{\sigma_s(A_{wp} - A_{wf})}{W_n} \tag{23}$$

where σ_s is the specific surface or surface per unit area, A_{wp} and A_{wf} are the areas per unit mass of product particulates and feed particulates, i.e., after and before milling, respectively, and W_n is the energy absorbed by the solid, per unit mass. The energy absorbed by the solid, per unit mass, is less than the energy W supplied to the mill, per unit mass, i.e., $W_n < W$. While a substantial part of the total energy input W is needed to overcome friction in the machine, the rest is available for crushing or grinding. However, only a small fraction of the total energy stored within a solid is converted into surface energy at the time of fracture. As most of the energy is converted

[o] Total elapsed milling time encompasses the time during which solids are subjected to a milling operation, whether the particulates undergo single or multiple passes through the mill.

into heat, crushing efficiency values tend to be low, i.e., $0.0006 \leq E_c \leq 0.01$, principally due to the inexactness of estimates of σ_s (45).

A number of quasitheoretical relationships have been proposed to characterize the grinding process, including Rittinger's "law" (1867),

$$\frac{P}{\dot{m}} = K_R \left(\frac{1}{\overline{D}_p} - \frac{1}{\overline{D}_f} \right) \tag{24}$$

which states that that the work required to crush a solid is proportional to the new surface created, and Kick's "law" (1867),

$$\frac{P}{\dot{m}} = K_K \ \ln \frac{\overline{D}_f}{\overline{D}_p} \tag{25}$$

which states that the work required to crush or grind a given mass of material is constant for the same particle size reduction ratio. In Equations (24) and (25), $\overline{D}_p$ and $\overline{D}_f$ represent the final and initial average particle sizes,[p] P is the power (in kW), and $\dot{m}$ is the rate at which solids are fed to the mill (in tons/hr). K_R and K_K are constants for the Rittinger equation and the Kick equation, respectively.

Bond's "law" of particle size reduction provides an ostensibly more reasonable estimate of the power required to crush or grind a solid (46)

$$\frac{P}{\dot{m}} = \frac{K_B}{\sqrt{D_P}} \tag{26}$$

where K_B is a constant which is *mill*-dependent and *solids*-dependent, and D_p is the particle size (in mm), produced by the mill. This empirical equation is based on Bond's hypothesis that the work required to reduce very large particulate solids to a smaller size is proportional to the square root of the surface to volume ratio of the resultant particulate product. Bond's work index, W_i, is an estimate of the gross energy required, in kilowatt hours per ton of feed, to reduce very large particles (80% of which pass a mesh size of D_f mm) to such a size that 80% pass through a mesh of size D_p mm:

$$W_i = \frac{K_B}{\sqrt{D_p}} \tag{27}$$

Combining Bond's work index [Eq. (27)] with Bond's law [Eq. (26)] yields

$$\frac{P}{\dot{m}} = W_i \bullet \sqrt{D_P} \left(\frac{1}{\sqrt{D_p}} - \frac{1}{\sqrt{D_f}} \right) \tag{28}$$

[p] In this section, particle size refers to the nominal particle size, i.e., the particle size based on sieving studies or on the diameter of a sphere of equivalent volume.

which allows one to estimate energy requirements for a milling operation in which solids are reduced from size D_f to D_p. [N.B. W_i for wet grinding is generally smaller than that for dry grinding: $W_{i,wet}$ is equivalent to $(W_{i,dry})^{3/4}$ (45)]

These relationships are embodied in the general differential equation

$$dE = -C\,dX/X^n \tag{29}$$

where E is the work done and C and n are constants. When $n = 1$, the solution of the equation is Kick's law; when $n = 2$, the solution is Rittinger's law; and, when $n = 1.5$, the solution is Bond's law (47).

Although these relationships [Eqs. (24)–(29)] are of some limited use in scaling-up milling operations, their predictability is limited by the inherent complexity of particle size reduction operations. Virtually all retentive or multiple pass milling operations become decreasingly efficient as milling proceeds because the specific comminution rate is smaller for small particles than for large particles. Computer simulations of milling for batch, multiple pass, and continuous modes have been outlined by Snow et al. (48). They describe a differential equation for batch grinding for which analytical and matrix solutions have been available for some time:

$$\frac{dw_k}{dt} = \sum_{u=1}^{k} \left[w_u S_u(t) \Delta B_{k,u} \right] - S_k(t) w_k \tag{30}$$

Equation (30) includes a term S_u, a grinding-rate function that corresponds to

$$S_u = -\frac{dw_u/dt}{w_u} \tag{31}$$

i.e., the rate at which particles of upper size u are selected for breakage per unit time relative to the amount, w_u, of size u present, and a term $\Delta B_{k,u}$, a breakage function that characterizes the size distribution of particle breakdown from size u intro all smaller sizes k. Equation (30) thus defines the rate of accumulation of particles of size k as the difference between the rate of production of particles of size k, from all larger particles, and the rate of breakage of particles of size k into smaller particles. Adaptation of Equation (30) to continuous milling operations necessitates the inclusion of the distribution of residence time, $\tau = M/F$, as discussed above.

Additional complications in milling arise as fines build up in the powder bed (43): (1) the fracture rate of *all* particle sizes decreases, the result, apparently, of a cushioning effect by the fines which minimizes stress and fracture; (2) fracture kinetics become non-linear. Other factors, such as coating of equipment surfaces by fines, also affect the efficiency of the milling operation.

Nonetheless, mathematical analyses of milling operations, particularly for ball mills, roller mills, and fluid energy mills, have been moderately successful. There continues to be a pronounced need for more complete understanding of micromeritic characteristics, the intrinsic nature of the milling operation itself, the influence of fines on the milling operation, and phenomena including flaw structure of solids, particle fracture, particulate flow, and interactions at both macroscopic and microscopic scales.

Mass Transfer

Movement of liquids and semisolids through conduits or pipes from one location to another is accomplished by inducing flow with the aid of pumps. The induction of flow usually occurs as a result of one or more of the following energy transfer mechanisms: gravity, centrifugal force, displacement, electromagnetic force, mechanical impulse, and momentum transfer. The work expended in pumping is the product of pump capacity, Q, i.e., the rate of fluid flow through the pump (in m^3/h), and the dynamic head, H:

$$P = \frac{HQ\rho}{3.670 \times 10^5} \tag{32}$$

where P is the pump's power output, expressed in kW, H the total dynamic head in N/m/kg, and ρ is the fluid density, in kg/m^3. Due to frictional heating losses, power input for a pump is greater than its power output. As pump efficiency is characterized by the ratio of power output to power input, the pumping of viscous fluids would tend to result in decreased pump efficiency due to the increase in power required to achieve a specific output. Another variable, ε, the surface roughness of the pipe, has an effect on pump efficiency as well and must also be considered. The Fanning friction factor f is a dimensionless factor that is used in conjunction with the Reynolds number to estimate the pressure drop in a fluid flowing in a pipe or conduit. The relative roughness, ε/D, of a pipe—where D is the pipe diameter—has an effect on the friction factor f. When *laminar* flow conditions prevail, f may be estimated by

$$f = \frac{16}{N_{\mathrm{Re}}} \tag{33}$$

When *turbulent* flow in smooth pipes is involved,

$$f = \frac{0.079}{(N_{\mathrm{Re}})^{0.25}} \tag{34}$$

A useful discussion of incompressible fluid flow in pipes and the influence of surface roughness and friction factors on pumping is found in *Perry's Chemical Engineer's Handbook* (49).

The transfer of material from mixing tanks or holding tanks to processing equipment or to a filling line, whether by pumping or by gravity-feed, is

potentially problematic. Instability (chemical or physical) or further processing, (e.g., mixing; changes in the particle size distribution) may occur during the transfer of material (by pouring or pumping) from one container or vessel to another due to changes in the rate of transfer or in shear rate or shear stress. While scale-up related changes in the velocity profiles of time-*independent* Newtonian and non-Newtonian fluids due to changes in flow rate or in equipment dimensions or geometry can be accounted for, time-dependency must first be recognized in order to be accommodated.

Changes in mass transfer *time* as a consequence of scale-up are often overlooked. As Carstensen and Mehta (50) note, mixing of formulation components in the laboratory may be achieved almost instantaneously with rapid pouring and stirring. They cite the example of pouring 20 mL of liquid A, while stirring, into 80 mL of liquid B. On a production scale, however, mixing is unlikely to be as rapid. A scaled-up batch of 2000 L would require the admixture of 400 L of A and 1600 L of B. If A were pumped into B at the rate of 40 L/min, then the transfer process would take at least 10 minutes, while additional time would also be required for the blending of the two liquids. If, for example, liquids A and B were of different pH (or ionic strength, polarity, etc.), the time required to transfer all of A into B and to mix A and B intimately would allow some intermediate pH (or ionic strength, polarity, etc.) to develop and persist, long enough for some adverse effect to occur, such as precipitation, adsorption, change in viscosity, etc. Thus, transfer times on a production scale need to be determined so that the temporal impact of scale-up can be accounted for in laboratory or pilot plant studies.

Dissolution

When dissolution is a necessary part of a manufacturing process, the ultimate objective—the formation of a homogeneous solution—can only be achieved through mixing of solute and solvent. Dissolution or mass transfer from the solute phase to a well-mixed solution phase may be characterized by a mass transfer coefficient, k, that relates the interfacial flux, j_i, or the amount of mass transferred per unit time per unit area, to the concentration difference between the bulk solution and the solution in the interfacial phase, i.e., immediately adjacent to the solute/solvent interface. That is, $k = (j_i)/\Delta C$. Most dissolution processes involve a turbulent flow regime in order to enhance the rate of mass transfer per unit area. For relatively large particles, the rate of increase in k is exponentially related to the increase in agitation intensity, i.e., $k \propto N^p$, where N is the impeller speed (rpm) and the exponent p may range from 0.1 to 0.8, depending upon the solid and liquid characteristics and the type and dimensions of the mixing tank and the impeller (51). As solute particles undergo dissolution, particle size decreases and fluid flow in the vicinity of the particles becomes laminar. As a result, k becomes independent of agitation intensity and diffusivity becomes the principal determinant of dissolution.

Maximal dissolution occurs when the contact between the dissolving solute and the dissolution medium is maximal. Thus, as dissolution is hampered when solute particles settle to the bottom of the tank, off-bottom suspension or fluidization of solute particles facilitates dissolution. Solid suspension in the fluid is the result of the drag and lift forces of the fluid on the solid particles and the turbulent eddies that result from the agitation imparted to the system. When complete off-bottom suspension is achieved, all particles remain suspended in the fluid or do not remain on the bottom of the tank for more than one or two seconds (51). Further increases in agitation intensity beyond this "just-suspended" state do not result in a corresponding increases in k as the accompanying increases in interfacial contact between solute and solvent are relatively small. Dead zones in the mixing tank (where particles tend to accumulate) are more apt to occur at the conjunction of the tank wall and tank base in a flat-bottomed mixing tank than in a dish-bottomed mixing tank.

Heat Transfer

On a laboratory scale, heat transfer occurs relatively rapidly as the volume to surface area ratio is relatively small; cooling or heating may or may not involve jacketed vessels. However, on a pilot plant or production scale, the volume to surface area ratio is relatively large. Consequently, heating or cooling of formulation components or product takes a finite time during which system temperature, T°C, may vary considerably. Temperature-induced instability may be a substantial problem if a formulation is maintained at suboptimal temperatures for a prolonged period of time. Thus, jacketed vessels or immersion heaters or cooling units with rapid circulation times are an absolute necessity. Carstensen and Mehta (50) gave an example of a jacketed kettle with a heated surface of A cm^2, with inlet steam or hot water in the jacket maintained at a temperature T_0°C. The heat transfer rate ($\mathrm{d}Q/\mathrm{d}t$) in this system is proportional to the heated surface area of the kettle and the temperature gradient, $T_0 - T$ (i.e., the difference between the temperature of the kettle contents, T, and the temperature of the jacket, T_0), at time t

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = C_\mathrm{p}\left(\frac{\mathrm{d}T}{\mathrm{d}t}\right) = kA(T_0 - T) \tag{35}$$

where C_p is the heat capacity of the jacketed vessel and its contents and k is the heat transfer coefficient. If the initial temperature of the vessel is T_1°C, Equation (35) becomes

$$T_0 - T = (T_0 - T_1)e^{-at} \tag{36}$$

where $a = kA/C_\mathrm{p}$. The time t required to reach a specific temperature T_2 can be calculated from Equation (36), if a is known or estimated from time–temperature

curves for similar products processed under the same conditions. Scale-up studies should consider the effect of longer processing times at suboptimal temperatures on the physicochemical or chemical stability of the formulation components and the product. A further concern for disperse system scale-up is the increased opportunity in a multiphase system for non-uniformity in material transport (e.g., flow rates and velocity profiles) stemming from non-uniform temperatures within processing equipment.

HOW TO ACHIEVE SCALE-UP[q]

Full-scale tests using production equipment, involving no scale-up studies whatsoever, are sometimes resorted to when single phase low-viscosity systems are involved and processing is considered to be predictable and directly scalable. By and large, these are unrealistic assumptions when viscous liquids, dispersions or semisolids are involved. Furthermore, the expense associated with full-scale testing is substantial: commercial-scale equipment is relatively inflexible and costly to operate. Errors in full-scale processing involve large amounts of material. Insofar as most liquids or semisolids are concerned then, full-scale tests are *not* an option.

On the other hand, scale-up studies involving relatively low scale-up ratios and few changes in process variables are not necessarily a reasonable alternative to full-scale testing. For that matter, experimental designs employing minor, incremental, changes in processing equipment and conditions are unacceptable as well. These alternative test modes are inherently unacceptable as they consume time, an irreplaceable resource (52) that must be utilized to its maximum advantage. Appropriate process development, by reducing costs and accelerating lead times, plays an important role in product development performance. In *The Development Factory*: *Unlocking the Potential of Process Innovation*, author Gary Pisano (53) argues that while pharmaceuticals compete largely on the basis of product innovation, there is a hidden leverage in process development and manufacturing competence that provides a greater degree of freedom in developing products to more adroit organizations than to their less adept competitors. Although Pisano focuses on drug synthesis and biotechnology process scale-up, his conclusions translate effectively to the manufacturing processes for drug dosage forms and delivery systems. In effect, scale-up issues need to be addressed jointly by pharmaceutical engineers and formulators as soon as a dosage form or delivery system appears to be commercially viable. Scale-up studies should not be relegated to the final stages of product development, whether initiated at the behest of FDA

[q]Reprinted in part, with revisions and updates, by courtesy of Marcel Dekker, Inc. from L. H. Block, "Scale-up of disperse systems: Theoretical and practical aspects," in *Pharmaceutical Dosage Forms: Disperse Systems* (H. A. Lieberman, M. M. Rieger, and G. S. Banker, eds.), Vol. 3, 2nd ed., New York: Marcel Dekker, 1998:378–388.

(to meet regulatory requirements) or marketing and sales divisions (to meet marketing directives or sales quotas). The worst scenario would entail the delay of scale-up studies until after commercial distribution (to accommodate unexpected market demands).

Modular scale-up involves the scale-up of individual components or unit operations of a manufacturing process. The interactions among these individual operations comprise the potential scale-up problem, i.e., the inability to achieve sameness when the process is conducted on a different scale. When the physical or physicochemical properties of system components are known, the scalability of some unit operations may be predictable.

Known scale-up correlations thus may allow scale-up even when laboratory or pilot plant experience is minimal. The fundamental approach to process scaling involves mathematical modeling of the manufacturing process and experimental validation of the model at different scale-up ratios. In a paper on fluid dynamics in bubble column reactors, Lübbert and coworkers (54) noted:

> Until very recently fluid dynamical models of multiphase reactors were considered intractable. This situation is rapidly changing with the development of high performance computers. Today's workstations allow new approaches to ... modeling.

Insofar as the scale-up of pharmaceutical liquids (especially disperse systems) and semisolids is concerned, virtually no guidelines or models for scale-up have generally been available that have stood the test of time. Uhl and Von Essen (55), referring to the variety of rules of thumb, calculation methods, and extrapolation procedures in the literature, state, "Unfortunately, the prodigious literature and attributions to the subject [of scale-up] seemed to have served more to confound. Some allusions are specious, most rules are extremely limited in application, examples give too little data and limited analysis...." Not surprisingly, then, the trial-and-error method is the one most often employed by formulators. As a result, serendipity and practical experience continue to play large roles in the successful pursuit of the scalable process.

Principles of Similarity

Irrespective of the approach taken to scale-up, the scaling of unit operations and manufacturing processes requires a thorough appreciation of the principles of *similarity*. "Process similarity is achieved between two processes when they accomplish the same process objectives by the same mechanisms and produce the same product to the required specifications." Johnstone and Thring (56) stress the importance of four types of similarity in effective process translation: (1) geometric similarity; (2) mechanical (static, kinematic, and dynamic) similarity; (3) thermal similarity; and (4)

chemical similarity. Each of these similarities presupposes the attainment of the other similarities. In actuality, approximations of similarity are often necessary due to departures from ideality (e.g., differences in surface roughness, variations in temperature gradients, changes in mechanism, etc.). When such departures from ideality are not negligible, a correction of some kind has to be applied when scaling-up or -down: these scale effects must be determined before scaling of a unit operation or a manufacturing process can be pursued. It should be recognized that scale-up of multiphase systems, based on similarity, is often unsuccessful since only one variable can be controlled at a time, i.e., at each scale-up level. Nonetheless, valuable mechanistic insights into unit operations can be achieved through similarity analyses.

Geometric Similarity

Point-to-point geometric similarity of two bodies (e.g., two mixing tanks) requires three-dimensional correspondence. Every point in the first body is defined by specific x, y, and z coordinate values. The corresponding point in the second body is defined by specific x', y', and z' coordinate values. The correspondence is defined by the following equation:

$$\frac{x'}{x} = \frac{y'}{y} = \frac{z'}{z} = L \tag{37}$$

where the linear scale ratio L is constant. In contrasting the volume of a laboratory scale mixing tank (V_1) that of a geometrically similar production scale unit (V_2), the ratio of volumes (V_1/V_2) is dimensionless. However, the contrast between the two mixing tanks needs to be considered on a linear scale: e.g., a 1000-fold difference in volume corresponds to a 10-fold difference, on a linear scale, in mixing tank diameter, impeller diameter, etc.

If the scale ratio is not the same along each axis, the relationship among the two bodies is of a *distorted geometric similarity* and the axial relationships are given by

$$\frac{x'}{x} = X, \quad \frac{y'}{y} = Y, \quad \frac{z'}{z} = Z \tag{38}$$

Thus, equipment specifications can be described in terms of the scale ratio L or, in the case of a distorted body, two or more scale ratios (X, Y, Z). Scale ratios facilitate the comparison and evaluation of different sizes of functionally comparable equipment in process scale-up.

Mechanical Similarity

The application of force to a stationary or moving system can be described in static, kinematic, or dynamic terms that define the mechanical similarity of processing equipment and the solids or liquids within their confines. *Static* similarity relates the deformation under constant stress of one body

or structure to that of another; it exists when geometric similarity is maintained even as elastic or plastic deformation of stressed structural components occurs (56). In contrast, *kinematic* similarity encompasses the additional dimension of time while *dynamic* similarity involves the forces (e.g., pressure, gravitational, centrifugal, etc.) that accelerate or retard moving masses in dynamic systems. The inclusion of time as another dimension necessitates the consideration of *corresponding times*, t' and t, for which the time scale ratio $\mathbf{t}$, defined as $\mathbf{t} = t'/t$, is a constant.

Corresponding particles in disperse systems are geometrically similar particles which are centered on corresponding points at corresponding times. If two geometrically similar fluid systems are kinematically similar, their corresponding particles will trace out geometrically similar paths in corresponding intervals of time. Thus, their flow patterns will be geometrically similar and heat- or mass-transfer rates in the two systems will be related to one another (56). Pharmaceutical engineers may prefer to characterize disperse systems' *corresponding velocities*, which are the velocities of corresponding particles at corresponding times

$$\frac{v'}{v} = v = \frac{L}{\mathbf{t}} \tag{39}$$

Kinematic and geometric similarity in fluids ensures geometrically similar streamline boundary films and eddy systems. If forces of the same kind act upon corresponding particles at corresponding times, they are termed *corresponding forces*, and conditions for dynamic similarity are met. While the scale-up of power consumption by a unit operation or manufacturing process is a direct consequence of dynamic similarity, mass and heat transfer—direct functions of kinematic similarity—are only indirect functions of dynamic similarity.

Thermal Similarity

Heat flow, whether by radiation, conduction, convection, or the bulk transfer of matter, introduces temperature as another variable. Thus, for systems in motion, thermal similarity requires kinematic similarity. Thermal similarity is described by

$$\frac{H'_{\mathrm{r}}}{H_{\mathrm{r}}} = \frac{H'_{\mathrm{c}}}{H_{\mathrm{c}}} = \frac{H'_{\mathrm{v}}}{H_{\mathrm{v}}} = \frac{H'_{\mathrm{f}}}{H_{\mathrm{f}}} = \mathbf{H} \tag{40}$$

where H_{r}, H_{c}, H_{v}, and H_{f}, are the heat fluxes or quantities of heat transferred per second by radiation, convection, conduction, and bulk transport, respectively, and $\mathbf{H}$, the thermal ratio, is a constant. Geometric similarity is a necessary requirement as well and, insofar as thermal similarity is concerned, extends even to the thickness of tank walls, impeller shafts and blades, etc.

Chemical Similarity

This similarity state is concerned with the variation in chemical composition from point to point as a function of time. Chemical similarity, i.e., the existence of comparable concentration gradients, is dependent upon both thermal and kinematic similarity.

Interrelationships Among Surface Area and Volume Upon Scale-up

Similarity states aside, the dispersion technologist must be aware of whether a given process is volume-dependent or area-dependent. As the scale of processing increases, volume effects become increasingly more important while area effects become increasingly less important. This is exemplified by the dependence of mixing tank volumes and surface areas on scale-up ratios (based on mixing tank diameters) in Table 1 [adapted from Tatterson (57)]. The surface area to volume ratio is much greater on the small scale than on the large scale: surface area effects are thus much more important on a small scale than on a large one. Conversely, the volume to surface area ratio is much greater on the large scale than on the small scale: volumetric effects are thus much more important on a large scale than on a small scale. Thus, volume-dependent processes are more difficult to scale-up than surface area-dependent processes. For example, exothermic processes may generate more heat than can be tolerated by a formulation, leading to undesirable phase changes or product degradation unless cooling coils, or other means of intensifying heat transfer, are added. A further example is provided by a scale-up problem involving a 10-fold increase in tank volume, from 400 to 4000 L, and an increase in surface area from 2 to 10 m^2. The surface area to volume ratio is 1/200 and 1/400, respectively. In spite of the 10-fold increase in tank volume, the increase in surface area is only fivefold, necessitating the provision of additional heating or cooling capacity to allow for an additional 10 m^2 of surface for heat exchange.

As Tatterson (57) notes, "there is much more volume on scale-up than is typically recognized. This is one feature of scale-up that causes more difficulty than anything else." For disperse systems, a further mechanistic

Table 1 Area- and Volume-Dependence on Scale-Up Ratios

Scale	Tank diam. (m)	Area (m^2)	Volume (m^3)	Area/volume	Volume/area
1	0.1	0.0393	0.000785	50	0.02
10	1	3.93	0.785	5	0.2
20	2	15.7	6.28	2.5	0.4
50	5	98.2	98.2	1	1

Assumptions: Tank is a right circular cylinder; batch height = tank diameter; area calculations are the sum of the area of the convex surface and the area of the bottom of the cylinder.

implication of the changing volume and surface-area ratios is that particle size reduction (or droplet breakup) is more likely to be the dominant process on a small scale while aggregation (or coalescence) is more likely to be the dominant process on a large scale (57).

Interrelationships Among System Properties Upon Scale-up

When a process is dominated by a mixing operation, another gambit for the effective scale-up of geometrically similar systems involves the interrelationships that have been established for impeller-based systems. Tatterson (58) describes a number of elementary scale-up procedures for agitated tank systems that depend upon operational similarity. Thus, when scaling up from levels 1 to 2,

$$\frac{(P/V)_1}{(P/V)_2} = \begin{cases} \left(\frac{N_1}{N_2}\right)^3 \left(\frac{D_1}{D_2}\right)^2 & \text{for turbulent flow} \\ \left(\frac{N_1}{N_2}\right)^2 & \text{for laminar flow} \end{cases} \tag{41}$$

power per unit volume is dependent principally on the ratio N_1/N_2 since impeller diameters are constrained by geometric similarity.

A change in size on scale-up is not the sole determinant of the scalability of a unit operation or process. Scalability depends on the unit operation mechanism(s) or system properties involved. Some mechanisms or system properties relevant to dispersions are listed in Table 2 (59). In a number of instances, size has little or no influence on processing or on system behavior. Thus, scale-up will not affect chemical kinetics or thermodynamics although the thermal effects of a reaction could perturb a system, e.g., by affecting convection (59). Heat or mass transfer within or between phases is indirectly affected by changes in size while convection is directly

Table 2 Influence of Size on System Behavior or Important Unit Operation Mechanisms

System behavior or unit operation mechanisms	Important variables	Influence of size
Chemical kinetics	C, P, T	None
Thermodynamic properties	C, P, T	None
Heat transfer	Local velocities, C, P, T	Important
Mass transfer within a phase	N_{Re}, C, T	Important
Mass transfer between phases	Relative phase velocities, C, P, T	Important
Forced convection	Flow rates, geometry	Important
Free convection	Geometry, C, P, T	Crucial

Abbreviations: C, concentration; P, pressure; T, temperature.
Source: Adapted from Ref. 59.

affected. Thus, since transport of energy, mass, and momentum are often crucial to the manufacture of disperse systems, scale-up can have a substantial effect on the resultant product.

Dimensions, Dimensional Analysis, and the Principles of Similarity

Just as process translation or scaling-up is facilitated by defining similarity in terms of dimensionless ratios of measurements, forces, or velocities, the technique of dimensional analysis per se permits the definition of appropriate composite dimensionless numbers whose numeric values are process-specific. Dimensionless quantities can be pure numbers, ratios, or multiplicative combinations of variables with no net units.

Dimensional analysis is concerned with the nature of the relationship among the various quantities involved in a physical problem. An intermediate approach between formal mathematics and empiricism, it offers the pharmaceutical engineer an opportunity to generalize from experience and apply knowledge to a new situation (60,61). This is a particularly important avenue as many engineering problems—scale-up among them—cannot be solved completely by theoretical or mathematical means. Dimensional analysis is based on the fact that if a theoretical equation exists among the variables affecting a physical process, that equation must be dimensionally homogeneous. Thus, many factors can be grouped in an equation into a smaller number of dimensionless groups of variables (61).

Dimensional analysis is an algebraic treatment of the variables affecting a process; it does not result in a numerical equation. Rather, it allows experimental data to be fitted to an empirical process equation which results in scale-up being achieved more readily. The experimental data determine the exponents and coefficients of the empirical equation. The requirements of dimensional analysis are that: (1) only one relationship exists among a certain number of physical quantities; and (2) no pertinent quantities have been excluded nor extraneous quantities included.

Fundamental (primary) quantities that cannot be expressed in simpler terms include mass (M), length (L), and time (T). Physical quantities may be expressed in terms of the fundamental quantities: e.g., density is ML^{-3}; velocity is LT^{-1}. In some instances, mass units are covertly expressed in terms of force (F) in order to simplify dimensional expressions or render them more identifiable. The MLT and FLT systems of dimensions are related by the equations

$$F = Ma = \frac{ML}{T^2}$$

$$M = \frac{FT^2}{L}$$

According to Bisio (62), scale-up can be achieved by maintaining the dimensionless groups characterizing the phenomena of interest constant from small scale to large scale. However, for complex phenomena, this may not be possible. Alternatively, dimensionless numbers can be weighted so that the untoward influence of unwieldy variables can be minimized. On the other hand, this camouflaging of variables could lead to an inadequate characterization of a process and a false interpretation of laboratory or pilot plant data.

Pertinent examples of the value of dimensional analysis have been reported in a series of papers by Maa and Hsu (19,37,63). In their first report, they successfully established the scale-up requirements for microspheres produced by an emulsification process in continuously stirred tank reactors (CSTRs) (63). Their initial assumption was that the diameter of the microspheres, d_{ms}, is a function of phase *quantities*, *physical properties* of the dispersion and dispersed phases, and *processing equipment parameters*:

$$d_{\mathrm{ms}} = f\left(D\omega, D/T, H, B, n_{\mathrm{imp}}, g_{\mathrm{c}}, g, c, \eta_o, \eta_a, \rho_o, \rho_a, v_o, v_a, \sigma\right) \tag{42}$$

Gravitational acceleration, g, is included to relate mass to inertial force. The conversion factor, g_{c}, was included to convert one unit system to another. The subscripts o and a refer to the organic and aqueous phases, respectively. The remaining notation is as follows:

D	impeller diameter (cm)
ω	rotational speed (angular velocity) of the impeller(s) (s^{-1})
T	tank diameter (cm)
H	height of filled volume in the tank (cm)
B	total baffle area (cm^2)
n	number of baffles
n_{imp}	number of impellers
v_o, v_a	phase volumes (mL)
C	polymer concentration (g/mL)
η_o and η_a	phase viscosities (g/cm/s)
ρ_o and ρ_a	phase densities (g/mL)
σ	interfacial tension between organic and aqueous phases (dyne/cm).

The initial emulsification studies employed a 1 L "reactor" vessel with baffles originally designed for fermentation processes. Subsequent studies were successively scaled up from 1 L to 3, 10, and 100 L. Variations due to differences in reactor configuration were minimized by utilizing geometrically similar reactors with approximately the same D/T ratio (i.e., 0.36–0.40). Maa and Hsu contended that separate experiments on the effect of the baffle area

(B) on the resultant microsphere diameter did not significantly affect d_{ms}. However, the number and location of the impellers had a significant impact on d_{ms}. As a result, to simplify the system, Maa and Hsu always used double impellers ($n_{\text{imp}} = 2$), with the lower one placed close to the bottom of the tank and the other located in the center of the total emulsion volume. Finally, Maa and Hsu determined that the volumes of the organic and aqueous phases, in the range they were concerned with, played only a minor role in affecting d_{ms}. Thus, by the omission of D/T, B, and v_o and v_a, Equation (42) was simplified considerably to yield

$$d_{\text{ms}} = f(D\omega, g_{\text{c}}, g, c, \eta_o, \eta_a, \rho_o, \rho_a\sigma) \tag{43}$$

Equation (43) contains 10 variables and four fundamental dimensions (L, M, T, and F). Maa and Hsu were able subsequently to define microsphere size, d_{ms} in terms of the processing parameters and physical properties of the phases:

$$\frac{g(\rho_o - \rho_a)d_{\text{ms}}^2}{\sigma} = \Pi_2^{-0.280}\Pi_3^{-0.108}\Pi_4^{-0.056}\left(0.0255\Pi_5^e + 0.0071\right) \tag{44}$$

where Π_i are dimensionless multiplicative groups of variables. [The transformation of Equation (43) into Equation (44) is described by Maa and Hsu (63) in an appendix to their paper.] Subsequently, linear regression analysis of the microsphere size parameter, $g(\rho_o - \rho_a)d_{\text{ms}}^2/\sigma$, as a function on the right-hand side of Equation (43), i.e., $\left[\Pi_2^{-0.280}\Pi_3^{-0.108}\Pi_4^{-0.056}\left(0.0255\Pi_5^e + 0.0071\right)\right]$, resulted in $r \approx 0.973$ for 1, 3, 10, and 100 L reactors, at two different polymer concentrations. These composite data are depicted graphically in Figure 3.

Subsequently, Maa and Hsu (19) applied dimensional analysis to the scale-up of a liquid–liquid emulsification process for microsphere production, utilizing one or another of three different static mixers which varied in diameter, number of mixing elements, and mixing element length. Mixing element design differences among the static mixers were accommodated by the following equation:

$$d_{\text{ms}} = 0.483d^{1.202}V^{-0.556}\sigma^{0.556}\eta_a^{-0.560}\eta_o^{0.004}n^h c^{0.663} \tag{45}$$

where d_{ms} is the diameter of the microspheres (μm) produced by the emulsification process, d the diameter of the static mixer (cm), V the flow rate of the continuous phase (mL/sec), σ is the interfacial tension between the organic and aqueous phases (dyne/cm), η_a and η_o are the viscosities (g/cm/sec) of the aqueous and organic phases, respectively, n is the number of mixing elements, h is an exponent the magnitude of which is a function of static mixer design, and c is the polymer concentration (g/mL) in the organic phase. The relative efficiency of the three static mixers was readily determined in terms of emulsification efficiency, ε defined as equivalent to

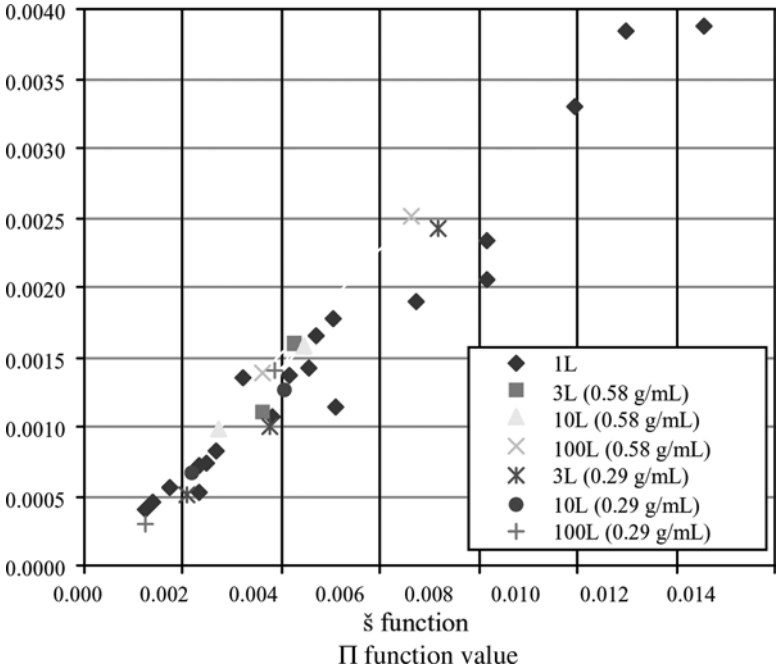

Figure 3 Microsphere diameter parameter, d_{ms}, as a function of processing parameters and physical properties of the phases. *Source*: Π Functions on the right-hand side of Eq. (31), after Ref. 61.

$1/d_{ms}$: better mixing results in smaller microspheres. In this way, Maa and Hsu were able to compare and contrast continuously stirred tank reactors (CSTRs) with static mixers.

Houcine et al. (64) used a non-intrusive laser-induced fluorescence method to study the mechanisms of mixing in a 20 dm^3 CSTR with removable baffles, a conical bottom, a mechanical stirrer, and two incoming liquid jet streams. Under certain conditions, they observed an interaction between the flow induced by the stirrer and the incoming jets, which led to oscillations of the jet stream with a period of several seconds and corresponding switching of the recirculation flow between several metastable macroscopic patterns. These jet feedstream oscillations or intermittencies could strongly influence the kinetics of fast reactions, such as precipitation. The authors used dimensional analysis to demonstrate that the intermittence phenomenon would be less problematic in larger CSTRs.

Additional insights into the application of dimensional analysis to scale-up can be found in the chapter in this volume by Zlokarnik (65) and in his earlier monograph on scale-up in chemical engineering (66).

Mathematical Modeling and Computer Simulation

Basic and applied research methodologies in science and engineering are undergoing major transformations. Mathematical models of "real-world" phenomena are more elaborate than in the past, with forms governed by sets of partial differential equations, that represent continuum approximations to microscopic models (67). Appropriate mathematical relationships would reflect the fundamental laws of physics regarding the conservation of mass, momentum, and energy. Euzen et al. (68) list such balance equations for mass, momentum, and energy (e.g., heat) for a single-phase Newtonian system (with constant density, ρ, viscosity, η, and molar heat capacity at constant pressure, C_p) in which a process takes place in an element of volume, ΔV (defined as the product of dx, dy, and dz):

$$\frac{\partial C_i}{\partial t} = -\left\{\nu_x \frac{\partial C_i}{\partial x} + \nu_y \frac{\partial C_i}{\partial y} + \nu_z \frac{\partial C_i}{\partial z}\right\} + \left\{D_{ix} \frac{\partial^2 C_i}{\partial x^2} + D_{iy} \frac{\partial^2 C_i}{\partial y^2} + D_{iz} \frac{\partial^2 C_i}{\partial z^2}\right\} + R_i$$

Mass Balance

$$\rho\left\{\frac{\partial \nu_x}{\partial t} + \nu_x \frac{\partial \nu_x}{\partial x} + \nu_y \frac{\partial \nu_x}{\partial y} + \nu_z \frac{\partial \nu_x}{\partial z}\right\} = -\frac{\partial P}{\partial x} + \eta\left\{\frac{\partial^2 \nu x}{\partial x^2} + \frac{\partial^2 \nu_x}{\partial y^2} + \frac{\partial^2 \nu_x}{\partial z^2}\right\} + \rho g_x$$

Momentum Balance (e.g., in x direction)

$$\rho C_p\left\{\frac{\partial T}{\partial t} + \nu_x \frac{\partial T}{\partial x} + \nu_y \frac{\partial T}{\partial Y} + \nu_z \frac{\partial T}{\partial z}\right\} = \left\{k_x \frac{\partial^2 T}{\partial x^2} + k_y \frac{\partial^2 T}{\partial y^2} + k_z \frac{\partial^2 T}{\partial Z^2}\right\} + S_R$$

Energy Balance (46)

wherein P is pressure, T is temperature, t is time, v is fluid flow velocity, k is thermal conductivity, and R_i, g_x, and S_R are kinetic, gravitational, and energetic parameters, respectively. Equation (46) is presented as an example of the complex relationships that are becoming increasingly more amenable to resolution by computers, rather than for its express utilization in a scale-up problem. Pordal et al. (69) reviewed the potential role of computational fluid dynamics (CFD) in the pharmaceutical industry. Kukura et al. (70) and McCarthy et al. (71,72) have used CFD software to simulate the hydrodynamic conditions of the USP dissolution apparatus. Their results demonstrate the value of CFD in analyzing hydrodynamic conditions in mixing processes. A more extensive review of CFD can be found in the recent publication by Marshall and Bakker (73).

However, most CFD software programs available to date for simulation of transport phenomena require the user to define the model equations and parameters and specify the initial and boundary conditions in accordance with the program's language and code, often highly specialized. A practical interim solution to the computational problem presented by Equation (46) and its non-Newtonian counterparts is at hand now in the form of software developed by Visimix Ltd. (74)—VisiMix 2000 Laminar

and VisiMix 2000 Turbulent—for personal computers. These interactive programs utilize a combination of classical transport equations in conjunction with algorithms for computation of mixing processes and actual laboratory, pilot plant, and production data to simulate macro- and microscale transport phenomena. VisiMix's user-friendly, menu-driven software is based on physical and mathematical models of mixing phenomena based on fundamental transport equations and on extensive theoretical and experimental research (75–77). Graphical menus allow the user to select and define process equipment from a wide range of options including vessel shape, agitator type, jacketing, and baffle type. VisiMix not only addresses most unit operations with a mixing component (e.g., blending, suspension of solids, emulsification, dissolution, and gas dispersion) but also evaluates heat transfer/exchange (e.g., for jacketed tanks). Tangential velocity distributions, axial circulation, macro- and microscale turbulence, mixing time, equilibrium droplet size distribution, and droplet break-up and coalescence are just some of the calculations or simulations that VisiMix can provide.

Liu and Neeld (78) used VisiMix software to calculate shear rates in laboratory, pilot plant, and production scale vessels. Their results (Table 3) showed marked differences, by as much as two orders of magnitude, in the shear rates calculated in the conventional manner [from tip speed and the distance from impeller tip to baffle, i.e., $\dot{\gamma} = ND/(T - D)$] and the shear rates computed by VisiMix. The latter's markedly higher shear rates resulted from VisiMix's definition of the shear rate in terms of Kolmogorov's model of turbulence and the distribution of flow velocities. Note that VisiMix's estimates of the respective shear rates in the vicinity of the impeller blade are comparable at all scales while the shear rates in the bulk volume or near

Table 3 Shear Rates at Different Processing Scales

Scale	Agitator speed (rpm)	Tip velocity (m/S)	Average shear rate = (tip speed/ distance from tip to baffle) (1/s)	VisiMix simulation: shear rate in bulk volume (1/s)	VisiMix simulation: shear rate near impeller blade (1/s)	VisiMix simulation: shear rate near baffle (1/s)
Laboratory reactor	700	3.11	37	902	12,941	902
Pilot plant reactor	250	5.98	118	2,470	12,883	4,146
Production plant reactor	77	8.60	15	1,517	11,116	1,678

Source: Adapted from Ref. 78.

the baffle are not, except on the laboratory scale. If the efficacy of the mixing process were dependent upon the shear achieved adjacent to the impeller, the VisiMix scaling simulations would predict comparable outcomes for the equipment parameters employed. However, if the shear rate in the vicinity of the impeller were not the controlling factor in achieving similitude, then scale-up relying on adjustments in agitator speed or tip velocity would be unsuccesful.

Experimental Aspects

Tools and techniques for obtaining qualitative and quantitative measurements of mixing processes have been described and critiqued in detail by Brown et al. (79). Scale-up experimentation involving mixing in stirred tanks generally entails vessels between ~0.2 and 2 m in diameter. At the low end, geometric similarity may be difficult to achieve and probes may not be small enough to avoid altering flow patterns or fluid velocities, especially on a microscopic scale. Bubble, droplet, or particle sizes may also be of the same order of magnitude as the probes or equipment components (baffles, impellers, etc.), thereby decreasing the applicability of the experimental data to larger scale systems.

SCALE-UP PROBLEMS

As Baekland (80) said, "Commit your blunders on a small scale and make your profits on a large scale." Effective scale-up mandates an awareness of the relative importance of various process parameters at different scales of scrutiny. Heat transfer, molecular diffusion, and microscopic viscosity operate on a so-called microscopic scale. On a macroscopic scale, these parameters may not appear to have a noticeable effect, yet they cannot be ignored: were there no energy, mass, or momentum transport at the microscopic scale, larger scale processes would not function properly (57). On the other hand, a system's flow regimes operate at both the microscopic and macroscopic level. Turbulent flow, characterized by random swirling motions superimposed on simpler flow patterns, involves the rapid tumbling and retumbling of relatively large portions of fluid, or eddies. While turbulence, encountered to some degree in virtually all fluid systems, tends to be isotropic on a small scale, it is anisotropic on a large scale.

Ignoring or misinterpreting unit operations or process fundamentals. Among some of the more common scale-up errors are:

- scaling based on wrong unit operation mechanism(s),
- incompletely characterized equipment: e.g., multishaft mixers/homogenizers,
- insufficient knowledge of process; lack of important process information,

- utilization of different types of equipment at different levels of scale-up,
- unrealistic expectations (e.g., heat dissipation),
- changes in product or process (e.g., altered formulation, phase changes, changes in order of addition, etc.) during scale-up.

These last issues, in particular, are exemplified by the report of Williams et al. (81) on problems associated with the scale-up of an o/w cream containing 40% diethylene glycol monoethyl ether and various solid, waxy excipients (e.g., cetyl alcohol; polyoxyethylene-2-stearyl ether). Preparation of 300 g batches in the laboratory in small stainless steel beakers proceeded without incident while 7 kg batches made with a Brogli-10 homogenizer were subject to precipitation in or congealing of the external phase in the region between the sweep agitation blade and the discharge port. Low levels of congealed or precipitated excipient, which went undetected on the laboratory scale, marked differences in the rate and extent of heat exchange at the two levels of manufacturing, and the presence of cold spots or non-jacketed areas in the Brogli-10 homogenizer contributed to the problem.

Unfortunately, the publication by Williams and coworkers is one of the only reports of a scale-up problem involving liquids or semisolids in the pharmaceutical literature. A number of papers that purport to deal with scale-up issues and even go so far as to compare the properties of small versus large batches failed to apply techniques, such as dimensional analysis, that could have provided the basis for a far more substantial assessment or analysis of the scale-up problem for their system. Worse yet, there is no indication of how scale-up was achieved or what scale-up algorithm(s), if any, were used. Consequently, their usefulness, from a pedagogical point of view, is minimal. In the end, effective scale-up requires the complete characterization of the materials and processes involved and a critical evaluation of all laboratory and production data that may have some bearing on the scalability of the process.

CONCLUSIONS

Process scale-up of liquids and semisolids not only is an absolutely essential part of pharmaceutical manufacturing, but also is a crucial part of the regulatory process. The dearth of research publications to date must reflect either the avoidance of scale-up issues by pharmaceutical formulators and technologists due to their inherent complexity or a concern that scale-up experimentation and data constitute trade secrets that must not be disclosed lest competitive advantages be lost. The emergence of pharmaceutical engineering as an area of specialization and the advent of specialized software capable of facilitating scale-up have begun to change these attitudes.

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5

Scale-Up Considerations for Biotechnology-Derived Products

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INTRODUCTION

This chapter covers the general principles involved in the scale-up of biotechnology-derived products obtained from cell culture. The first two sections focus on technologies currently used in the manufacture of commercial products. The subsequent sections include a practical guide to process design and scale-up strategies typically used to translate process development into large-scale production of biological products.

Advantages of Biologics as Therapeutic Agents

The main advantage of biologics over traditional small molecule drugs is that biologics are usually proteins that can be normally found in the body. If the biology of these proteins is well understood, the regulatory approval is facilitated, as toxicology and immunogenicity could be demonstrated at a much faster pace than in traditional small drug product approval cycles. In addition, biologics offer the advantage of multiple sites of interaction between the drug and the target, which is not usually possible to achieve with the use of small molecule drugs.

The introduction of biologics as credible therapies is evidenced by the increase in the approval rate of biologics over the last two decades. This is in contrast to the decline in the introduction of new small molecules (Fig. 1). The market potential of biologics is also projected to grow exponentially over the next few years (Fig. 2). These are some of the many drivers for

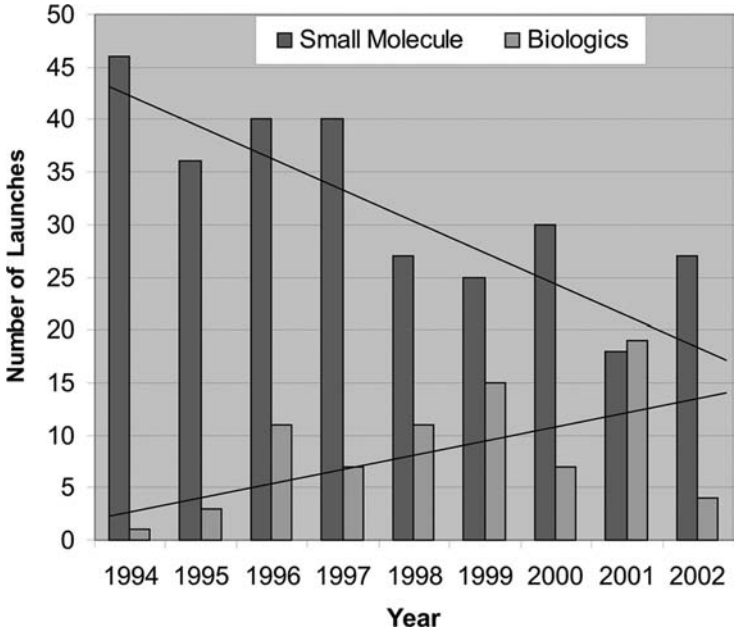

Figure 1 Trends in regulatory approvals of small molecule therapeutics versus biologics. *Source*: Adapted from Ref. 1.

the development of biologics, and the production methods of these molecules from cell culture will be covered in this chapter.

With increasing market demand for biotechnology-derived products, the global manufacturing capacity for cell culture at one point was estimated not to be able to meet the projected needs. However, within a few years, significant technology advancements in the areas of expression vectors, host cell lines, and media development have been made. For instance, expression levels for antibodies have gone up from less than 500 mg/L to over 5 g/L in cell culture. This improvement has made it possible not only to meet the demand with existing capacity but also to make biopharmaceutical production much more cost-effective.

In the case of protein separation technologies, further scale-up or multiple cycles will be needed until these challenges of increased throughput from cell culture are successfully met, for instance with, the use of improved resins having much higher binding capacities combined with good resolution.

General Considerations in the Development and Scale-Up of Cell Culture Processes

One obvious reason for scale-up in biologics is to meet market demand. Usually, small lots of product are produced during early evaluation of the

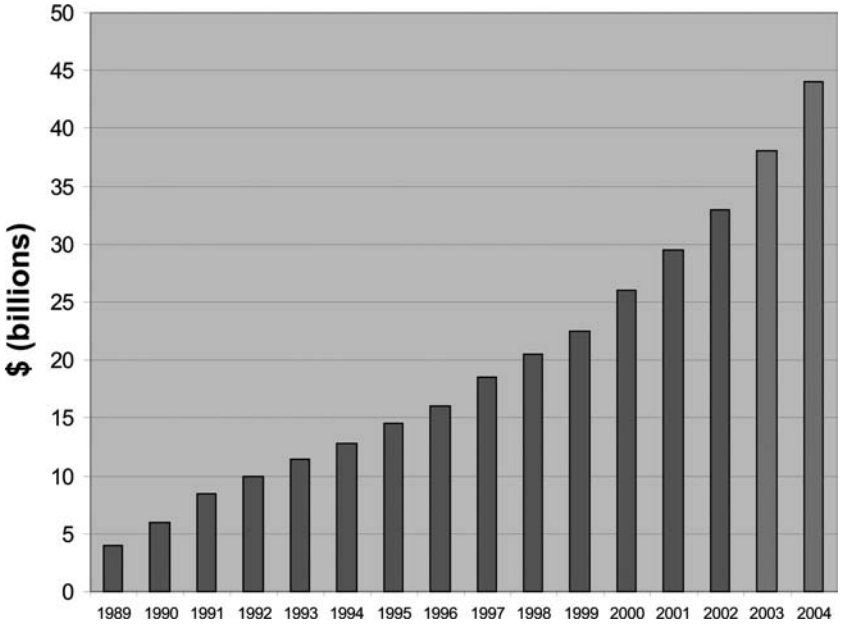

Figure 2 The biotech industry revenue projections. *Source*: 2002 data from Ref. 2.

drug, as the cost of manufacturing can be quite onerous. As the product candidate advances in clinical trials, more material is required and increases in scale of production or yield in the process, or both, are usually implemented. Another powerful reason to scale-up is to decrease the cost of manufacturing. Both the scale of manufacturing, and process improvement, regardless of the scale of manufacturing, have a profound effect on the direct cost of manufacturing, as shown in Figure 3.

If the product candidate is considered to be promising, then the next phase of planning is perhaps the most challenging one: when to scale-up and to what scale. Figure 4 can be used to make an estimation of production scale for a batch-based process, depending upon estimated product demand and process yield.

This decision to scale-up is usually made two to three years before the projected regulatory filing date for the approval of the product, which in turn means about three to four years before the launch of the product. This is why the decision to scale-up is in direct opposition to the process development timeline, and special care has to be taken when developing a process for biologics in order for manufacturing not to be limitation on product approval.

In addition to basic engineering design principles, the scale-up of biotechnology products requires an understanding of the cellular and regulatory mechanisms that govern cell physiology and the biophysical

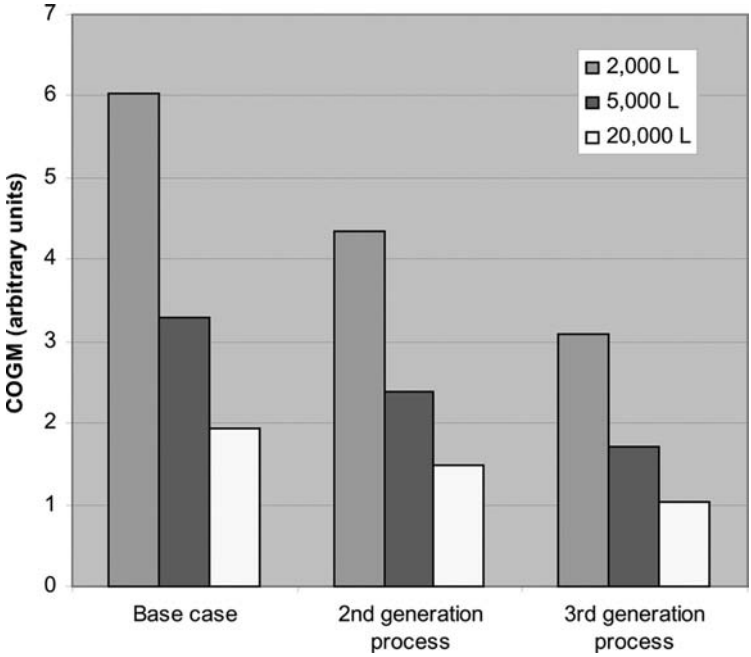

Figure 3 The impact of process scale and yield on direct cost of manufacturing.

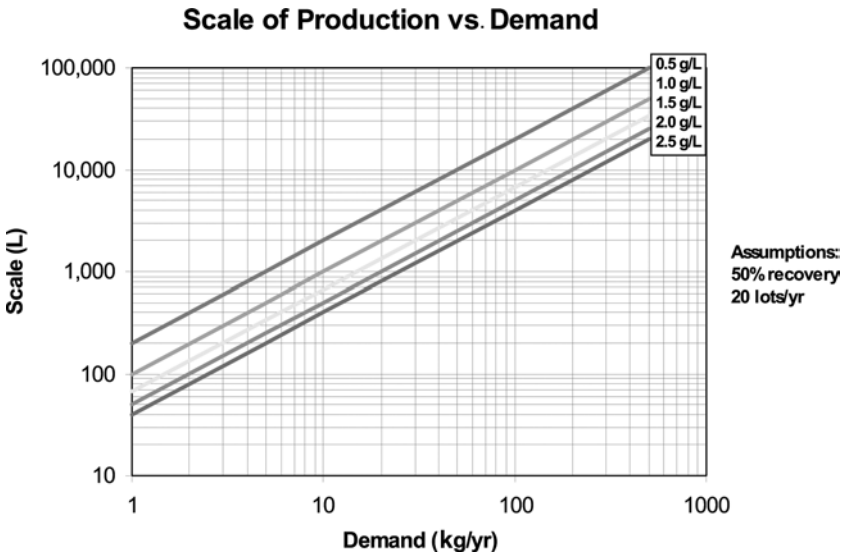

Figure 4 Scale of manufacturing as a function of product demand and cell culture yield.

and biochemical characteristics of products. A thorough understanding of process operations and process limitations is essential for successful technology transfer from development to manufacturing. The design and operation of the facility, including appropriate segregation of products, personnel and equipment at each stage of manufacturing, must comply with current regulatory guidelines. The true measure of successful scale-up is validation of the process at the manufacturing scale and ultimate approval of the biopharmaceutical product.

Due to the complexity of biological systems and the physical and biochemical characteristics of the protein products, the design and scale-up of biological processes can be challenging. Batch sizes for the production of biotechnology-derived products can reach 10,000 L (3), 12,500 L (4,5), and up to 20,000 L (6). Although these scales of operation are often smaller than conventional bacterial or yeast fermentation, the high value of individual production lots requires careful planning and process control. For this reason, laboratory and pilot scale data together with actual experience are essential for the effective selection of scale-up strategies, equipment, and process parameters (7).

The efficient and timely completion of scale-up to commercial manufacturing is critical to biotechnology companies. In some cases, novel unit operations or techniques are required to achieve adequate expression, recovery, quality, or integrity of the product, which may not be feasible with more conventional techniques. However, this may cause costly delays in product approval because the use of new technologies may be associated with a greater degree of uncertainty as the scale of the operation increases. In addition, the ease of process validation may be an important factor influencing the selection between novel and conventional process techniques (4,8). For example, cell culture processes can be conducted either as a batch or as a continuous process. However, the time required to validate a continuous process may be longer than that for a batch process. As a consequence, this may impact the time required for preparation and submission of documents to regulatory agencies, as well as the time needed for review and approval. For many companies, the duration of clinical development and the strategy for efficacy studies may determine the difference between success in the marketplace and total failure.

The timelines needed to complete technology transfer may vary with the complexity of the process. A team composed of manufacturing and development personnel should be responsible for facility design or integration of a process into an existing facility. The team is also responsible for equipment specifications and defining the physical relationship of process operations in order to comply with regulatory standards. The team must be aware of the relevant scale-up criteria to be used because their misapplication can lead to significant performance differences between bench top and manufacturing plant scales (9). For this reason, stepwise scale-up is recommended. In addition, successful scale-up requires that manufacturing personnel be

properly trained on process requirements and good manufacturing practices to provide an efficient and seamless transition to commercial production within the shortest time possible.

Recent advances in safety, selectivity, quality, and integrity of molecules obtained from recombinant microorganisms and immortalized cell lines have provided a wide range of products used as therapeutic agents. Marketed biotechnology products can be classified into five categories (3): coagulation factors, enzymes, hormones and growth factors, molecular inhibitors/antagonists, and vaccines. Examples of marketed biotechnology products are presented in Table 1. This table illustrates the diversity of cell lines (bacteria, yeast, and mammalian cells) used to produce licensed products. In addition to the expression systems listed below, other expression systems, such as insect cells, plant cells, and transgenic animals and plants, are currently being evaluated at preclinical and clinical stages.

As seen in Table 1, most of the cell lines used to manufacture biologics employ recombinant cells, in particular CHO and myeloma cell lines, that can be optimized to express complex proteins at high yields and are amenable to scale-up. Current trends in the industry show that in addition to these cell lines, human cells lines such as HEK293 and PER.C6 (11), yeasts (12), and molds (13) could also be alternatives to express recombinant proteins. The incentive to use a human cell line is to mimic human proteins and to express recombinant proteins which otherwise could not be expressed in other cell lines. The use of yeast and fungi is intended to primarily decrease the cost of manufacturing as the manufacturing technology for these expression systems uses traditional fermentation techniques and state-of-the-art know-how to generate high cell density fermentations. In addition, significant advances have been made recently in yeast and fungi to express glycosylated proteins (12). It is expected that more data will be generated using these expression systems in the near future.

FUNDAMENTALS: TYPICAL UNIT OPERATIONS

Comprehensive descriptions of the basic unit operations commonly used in the production of biotechnology products are available in the literature (14). This section focuses on the typical unit operations currently used for production of biological molecules in cell culture and the technologies used for the purification of pharmaceutical proteins. For each of these operations, laboratory and pilot scale experiments provide the basis for scale-up, particularly to define the expected range of process operating parameters.

Bioreactor Operation

Commercial manufacturing operations in biotechnology usually employ bioreactors or fermentors for product expression. In this discussion, the term fermentor will refer to bacterial or fungal processes and the term bioreactor to animal cell cultures. While extensive description of the operation

Table 1 Examples of Biotechnology-Derived Products

Protein	Clinical application	Production process
Coagulation factors		
Recombinate (F VIII)[a]	Hemophilia	rCHO, bleed-feed
Kogenate (F VIII)[a]	Hemophilia	rBHK-21, bleed-feed
Novo Seven (F VIIa)[a]	Hemophilia A	rBHK
Bene Fix (FIX)[a]	Hemophilia B	rCHO
Enzymes		
Pulmozyme (Dnase I)[a]	Cystic fibrosis	rCHO, suspension
Cerezym[a]	Gaucher's disease	rCHO, microcarriers
Activase (tPA)[a]	Thrombolytic agent	rCHO, suspension
Abbokinase (Urokinase)	Pulmonary embolism	Human kidney cells
Aldurazyme (Laronidase)	Mucopolysaccharidosis I (MPS I)	
Cathflo Activase (Alteplase)	Restoration of function to central venous access devices	
Fabrazyme (Agalsidase beta)	Fabri disease	
Growth factor and hormones		
Welferon (IFN alfa)[a]	Hepatitis C treatment	Namalva
Roferon (IFN alfa-b)	Hepatitis C treatment	r*E.coli*
Infergen (IFN alfa)	Hepatitis C treatment	r*E.coli*
Intron A (IFN alfa)	Hairy cell lymphoma	r*E.coli*
Epogen (Epo)[a]	Stimulation of erithropoiesis	rCHO, Roller bottles
Avonex (IFN beta)[a]	Multiple sclerosis	rCHO
Betaseron (IFN beta)	Multiple sclerosis	r*E.coli*
Proleukin (IL)	Metastatic renal carcinoma	r*E.coli*
Gonal F (FSH)[a]	Induction of ovulation	rCHO
Saizen (hGH)[a]	Growth hormone deficiency	rC127, Roller bottles
PEGASYS (peginterferonalfa-2a)	Hepatitis C	
PEG-Intron (peginterferonalfa-2b)	Chronic hepatitis C	
Molecular inhibitors/antagonist		
Rituxan (Mab)	B-cell non-Hodgkin's lymphoma	rCHO
Synagis (Mab)	Prevention of RSV disease	rNS/0, suspension
Herceptin (Mab)	Breast cancer	rCHO, suspension
OKT3 (Mab)[a]	Rescue of acute renal rejection/GVHD	Mouse ascites
Zenapax (Mab)	Prevention of acute renal rejection	rNS/0, suspension
Reopro (Mab)	Prevention of cardiac ischemic complications	rSP2/0

(*Continued*)

Table 1 Examples of Biotechnology-Derived Products (*Continued*)

Protein	Clinical application	Production process
Leukine (GMCSF)	Induction chemotherapy for acute leukemia	ryeast
Neupogen (GCSF)	Treatment of neutropenia	r*E.coli*
Remicade (Mab)	Rheumatoid arthritis	rSP2/0
Enbrel	Rheumatoid arthritis	rCHO
Avastin (Mab)	Metastatic colorectal cancer	rCHO
Bexxar (Mab radioconjugate)	Non-Hodgkin's lymphoma	B cell
Zevalin (Mab radioconjugate)	Non-Hodgkin's lymphoma	B cell
Botox (Toxin)	Muscle relaxation activity, cervical dystonia	*Botulinum* sp.
Campath (Mab)	B-cell chronic lymphocytic leukemia	rCHO
Erbitux (Mab)	Metastatic colorectal cancer	SP2/0
Humira (Mab)	Rheumathoid arthritis	rCHO
Kinerect (Anakinra)	Rheumarthoid arthritis	r*E.coli*
MYOBLOC (*Botulinum* toxin type B)	Cervical dystonia	*Botulinum* sp.
Ontek (denileukin diftox)	Cutaneous T-cell lymphoma	r*E.coli*
Xoliar (Mab)	Metastatic colorectal cancer	rCHO
Vaccines		
Vaqta	Hepatitis A vaccine	MRC5 cells
Recombivax (HbsAg)	Hepatitis B vaccine	ryeast
Engerix-B (HbsAg)	Hepatitis B vaccine	ryeast
GenHevac B (HbsAg)[a]	Hepatitis B vaccine	rCHO, microcarriers
HB Gamma (HbsAg)[a]	Hepatitis B vaccine	rCHO
Comvax (HbsAg)	Combination of PedvaxHIB and Recombivax HB	Microbial fermentation
Infanrix	Tetanus toxoids, diphtheria, acellular pertussis vaccine	Bacterial fermentation
Certiva	Tetanus toxoids, diphtheria, acellular pertussis vaccine	Bacterial fermentation
LYMErix (OspA)	Lyme disease vaccine	r*E.coli*
RotaShield	Rotavirus vaccine	FRhk2
Varivax	Varicella vaccine	MRC5 cells
FluMist	Influenza virus vaccine	Eggs

[a]*Source*: Adapted from Ref. 10.

of fermentors and bioreactors is available elsewhere (9,14), this chapter will focus on bioreactors used in the manufacture of complex proteins.

There are a variety of types of bioreactors described in the literature. Among them, the stirred tank bioreactor is the most commonly employed

due to its performance record and ease of operation. Cells growing in bioreactors take up nutrients from the culture medium and release products, byproducts, and waste metabolites. Mass transport phenomena required for adequate supply of nutrients and removal of waste metabolites are greatly influenced by mixing and aeration rates. Agitation is used to maintain cells in suspension, to provide a homogeneous mix of nutrients, and to prevent the accumulation of toxic gases (15).

Aeration is also an essential requirement for aerobic cell lines. The design of aeration devices includes single-orifice tubes, sparger rings, and diffuser membranes. Bubble sizes may vary with each device and optimization is required to achieve the maximum ratio of surface area to gas volume transfer rate which generates a minimal of foaming to prevent damaging effects on cell viability (16,17). The effect of aeration on cell productivity is complex and depends on cell line, medium components (including cell proteins), and characteristics of foam formation and collapse. The optimal aeration rate then is determined empirically at each scale.

In the case of airlift bioreactors, air flowing upwards in a column-shaped bioreactor vessel is used to generate sufficient mixing of gases and cells simultaneously thereby replacing the need for conventional impellers of stirred tank bioreactors (18). High volume of airflow can result in foaming in this type of bioreactors, which can be suppressed with the addition of appropriate antifoam agents. The existing production scales in air-lift bioreactors are 2000 L and 5000 L.

Bioreactor technology also involves the application of single-use or "disposable" bioreactors, such as hollow fiber bioreactors, and more recently the concept of disposable stirred tank bioreactors up to the 2000 L scale has been introduced (19). This type of single use or disposable technology could make current stainless steel bioreactor equipment and facility design obsolete and may facilitate introduction of clinical stage manufacturing in a far more flexible format and faster than conventional hard-piped designs. This is an important innovation for minimizing capital expenditure, turn-around time from product campaigns, time to commissioning, and for facilitating concurrent product manufacturing.

Filtration Operations

Filtration technologies are used extensively throughout the biotechnology industry (20,21). Membranes and filters can be used for medium exchange during cell growth, cell harvest, product concentration, diafiltration, and formulation or for removal of viruses and control of bioburden. For example, micro filtration is used to replace spent medium with fresh medium (22) or to recover secreted proteins (5,22). Ultra filtration membranes with sub-micron pore sizes are used for product concentration and buffer exchange by diafiltration. Unlike in affinity capture step with Protein A where binding is very specific, for ion exchange capture steps preconditioning of cell culture

harvest by diafiltration into defined buffer composition can dramatically improve process consistency by providing more uniform load conditions.

Nanometer ultra filtration using filters with tightly controlled pore sizes can be used for virus removal (23). Filtration with 0.2 μm dead-end filters is used for removal of microorganisms (24). Sterilizing filters are validated for product-specific bubble point, product compatibility, and microbial retention. Depth filtration with disposable filter modules has been extensively used to clarify mammalian cell culture or to polish the clarified supernatants, due to ease of operation, high flow rates, and good product recoveries. Currently, charged depth filters with the added advantage of viral removal are entering into biotech processing, especially in the case of purification processes with limited viral clearance capability (25). Depth filters may also contribute to the removal of process contaminants, for example, DNA and endotoxin, and could be integrated into the process at various stages of the protein purification scheme. Due to the cost of these filters, it is preferable to use them wherever process volumes are low.

The key process parameters for filtration scale-up are trans-membrane pressure, filtration area, shear rate, operating time, temperature, flux rate, protein concentration, and solution viscosity (5).

Centrifugation

Centrifugation is used in fermentation processes as well as in blood serum fractionation. Scale-up of operations for separation of product-containing cells from supernatant fluid or secreted products from host cells is well established (26). Although batch centrifugation is often used at the laboratory scale, continuous centrifugation is preferred at the production scale. When centrifugation is used for biotechnology applications, it is preferable to use high-throughput low-shear centrifuges to minimize the shear sensitivity of animal cells. The centrifugation step is typically followed by depth-filtration to remove suspended solids not completely removed by centrifugal forces in order to minimize the impact of these molecules on downstream purification.

Filtration may be the preferable unit operation for separating secreted products from host cells because of the relatively mild operating conditions. A second advantage of filtration is that the cleaning validation is relatively simple compared to the elaborated cleaning validation required for continuous centrifuges. However, as the process volume increases, the economics of using filters decrease and space considerations increase in order to accommodate large filtration units. The operating cost and the increased complexity of operation of large filter units requiring high flow rates and with low shear make them unsuitable for very large-scale operations.

Because of the above considerations, it is preferred to use filtration as a clarification step for small scales (less than 2000 L of culture harvest), whereas centrifugation might be the choice for larger scales of operation.

Chromatography

Chromatography is a commonly used unit operation for the purification of proteins in biotechnology applications. It is capable of combining relatively high throughputs with high selectivity. A major advantage of this technique is that it can be optimized to achieve high resolution of the desired product from its contaminants. The selection of the appropriate gel* is very much dependent on an understanding of the physical and chemical characteristics of the target protein product. Chromatography steps can be designed to selectively either capture the product or remove contaminants. For ion exchange gels, contaminant removal is achieved by optimizing the pH and conductivity of the equilibration, wash, and elution buffers. Affinity chromatography is often used as an initial capture step to provide high specificity, high selectivity, and volume reduction. However, affinity chromatography gels, such as Protein A or Protein G, are costly, especially in early process steps with crude product streams. The use of crude material on affinity matrices may require extensive cleaning which contributes to the cost and can reduce the effective lifetime of the gel. Hydrophobic interaction chromatography (HIC), which takes advantage of different hydrophobicity of proteins and contaminants, also exhibits selectivity and specificity. Because proteins bind effectively to HIC gels at high conductivity, HIC can be integrated effectively with both ion exchange and affinity chromatography.

In addition, mixed mode resins, such as ceramic hydroxyapatite, which has both anion and cation exchange modes of separation, are commonly used as polishing steps. Advancements in resin chemistry are also leading to the implementation of shorter purification schemes with a limited number of in-process buffer exchange filtration steps. One such example is hydrophobic charge induction chromatography (HCIC). This resin is relatively less expensive but still selective for antibody binding compared to traditional affinity chromatography (27). Therefore, it can be used in place of costly Protein A resins to capture antibodies from process feed streams with high conductivity, such as fermentation or cell culture supernatants.

Key parameters for chromatography scale-up are gel capacity, linear velocity, buffer volume, bed height, temperature, cleanability, and gel lifetime.

Dimensional Analysis

Dimensional analysis is a useful tool for examining complex engineering problems by grouping process variables into sets that can be analyzed separately. If appropriate parameters are identified, the number of experiments needed for process design can be reduced and the results can be

* Definition: gel or resin are used interchangeably terms in the text to designate the chromatography matrix (fixed phase) used to purify proteins in solution.

described in simple mathematical expressions. In addition, the application of dimensional analysis may facilitate the scale-up for selected biotechnology unit operations. A detailed description of dimensional analysis is reviewed by Zlokarnik (28).

These analysis techniques provide a macroscopic description of the process and offer the possibility of qualitative assessment, although detailed mechanistic information is not captured. Due to the complexity of living systems, it may be impractical to provide a detailed description of the reaction parameters or to determine the specific dimensionless parameters for modeling cell growth and product production. However, models for mixing and aeration are well described in the literature. Similarly, for chromatography steps, it is often difficult to describe the purification of a single protein from a complex mixture of contaminants that range in concentration. However, parameters such as column volumes of solution (L solution per L of gel volume) may be used to maintain similarity between scales.

The scale-up of fermentors and bioreactors has been based on chemical industry methods for design and operation of chemical reactors. Most of the correlations used in the scale-up of fermentors and bioreactors pertain to mixing and aeration. Because agitation rates have a strong effect on cell culture performance, these rates must be optimized at each production scale. Although the effect of mechanical agitation on cell culture has been examined extensively (29,30), it should be noted that models describing mass transfer in agitated vessels are of limited value when scaling-up biological processes (12). While the experience available from fermentation technology has been adapted for scale-up of suspension cultures of animal cells, the scale-up of anchorage-dependent cell lines is more complicated (31) and will not be addressed here.

In a 1991 study by van Reis et al. (5), a filtration operation as applied to harvest of animal cells was optimized by the use of dimensional analysis. The fluid dynamic variables used in the scale-up work were the length of the fibers (L, per stage), the fiber diameter (D), the number of fibers per cartridge (n), the density of the culture (ρ), and the viscosity of the culture (μ). From these variables, scale-up parameters such as wall shear rate (γ_w) and its effect on flux ($L/m^2/h$) were derived. Based on these calculations, an optimum wall shear rate for membrane utilization, operating time, and flux was found. However, because there is no single mathematical expression relating all of these parameters simultaneously, the optimal solution required additional experimental research.

SCALE-UP OF UPSTREAM OPERATIONS

Unit operations for biological products obtained from fermentation or cell culture can largely be subdivided into four parts: medium preparation, inoculums expansion, bioreactor, and harvest operations.

Medium Preparation

In development or small clinical production runs, complete liquid medium may be most convenient. Economic issues may dictate that at large-scale powdered or liquid concentrate medium be used. Shipment and storage of large volumes of complete liquid medium is less practical at scales greater than 1000 L.

Culture medium is typically prepared by addition of the base powder or liquid concentrate mixtures to appropriate grade water. These base media mixtures usually contain amino acids, vitamins, cell membrane precursors, antioxidants, and growth factors, to mention some major categories of nutrients. Additional components, such as proteins or lipids, may need to be added separately since they are usually not compatible in powder blends.

At present, powdered medium is the formulation of choice for large-scale operations. Powdered medium is easy to ship and store, and has a longer shelf life compared to liquid formulations. Medium components are reduced in particle size by ball milling or micronization, mixed, and charged into appropriate sized containers. Regardless of which process is used to prepare the powder, homogeneity of the powder blend has always been a concern. Because each component will have a different particle size distribution, it may be difficult to be certain that each container of powder will have the exact same composition. Ray (32) reported on a study examining blend uniformity in powder medium production. A model powder was used to demonstrate homogeneity of medium components that are present at high (glucose) and low (phenol red) concentrations. Large drums of powdered medium were sampled from several locations within the drum to demonstrate homogeneity of amino acids. One issue that has not been adequately addressed yet is whether powder medium components settle and segregate during the course of shipping and storage.

Liquid concentrate medium has emerged recently as an alternative to powdered medium (33,34). For liquid concentrate preparation, medium components are grouped according to solubility criteria. Liquid medium concentrates allow for the preparation of medium in-line, by automated dilution of the concentrates with water of the appropriate quality (35). This would be particularly useful in continuous or perfused processes that require constant preparation of medium. Medium cost and component stability make it a secondary option for batch or fed-batch processes.

Cell Culture Inoculums Expansion

The objective of inoculums expansion is to increase the number of cells to an appropriate amount for inoculation of the production bioreactor. Cells are cultured in successively larger flasks by adding fresh medium during the exponential growth phase. Cells should be maintained in a rapidly growing state to ensure a vigorous culture for the production stage. If the cells in the culture are allowed to reach the plateau phase, growth of the culture may lag or cease

depending on the cell line and growth medium used. Each step of expansion is determined in laboratory experiments where culture growth curves are measured. There is a minimum seed cell density necessary to minimize the lag phase, as well as a maximum cell density to avoid losing the culture due to starvation or accumulation of toxic metabolites. In the case of fermentation of bacteria and fungi, the usual culture expansion ratio is one volume of inoculums to 10–100 volumes of fresh medium. In the case of animal cells, this ratio may be as low as one volume of inoculums to five volumes of fresh medium.

For the cultivation of animal cells, inoculums expansions have traditionally been conducted in T-flasks, shake flasks, spinner flasks, or roller bottles. Typically, T-flasks and shake flasks are used for smaller volumes at the beginning of inoculums expansion and roller bottles or spinner flasks for the larger volumes. However, one drawback of roller bottle inoculums expansion is that an increase in process scale requires an increase in the number of bottles, rather than an increase in the volume of the roller bottles, in order to keep the optimum surface to volume ratio. This approach, however, can quickly become cumbersome and labor-intensive. Unlike roller bottles, spinner flasks offer the convenience of using a larger size of flasks as the amount of inoculums increases. Thus, the number of inoculums vessels can be kept to a minimum, reducing the number of manipulations conducted under sterile conditions. However, it should be noted that in many cases the expansion of inoculums in these types of vessels might have significant oxygen transfer limitations. If larger flasks are to be used in the preparation of an inoculums train, an aeration strategy should be considered. Spinner flasks can be aerated either through the headspace or by sparging through a dip-tube. The inoculums can be expanded to 10–20 L using these types of flask systems. Beyond that volume, bioreactors of successively large volume will be used for expansion of the cells until the working volume of the production bioreactor is reached. An alternative method for inoculums expansion is to grow cells in a disposable plastic bag on a rocking platform (36). The bag can be configured with sterile hydrophobic filters to allow for aeration of the culture. Systems are currently available for culture volumes up to 100 L. Ultimately, the decision of choosing among the alternative methods will depend on cost, reliability, and confidence in the technique used to expand the inoculums.

One consideration to bear in mind during the design of inoculums expansion is to demonstrate the genetic stability of the cell line beyond the expected number of generations required to operate at large-scale. This is usually accomplished by conducting measurements of product expression and genetic markers in cells from an extended cell bank (ECB).

Bioreactor Operation

Several different bioreactor configurations have been described for use in cell culture and fermentation applications. These include stirred tanks,

airlift, and hollow fiber systems. The majority of bioreactor systems in use today for cell culture applications still have the stirred tank type.

Stirred Tank Bioreactor

It would not be possible to adequately cover the field of stirred tank scale-up in the space available here. Instead, this section will touch briefly on the important issues in bioreactor scale-up. For more detailed methodologies on stirred tank bioreactor scale-up, the reader is referred to several review papers on the topic (30,37,38).

As a stirred tank bioreactor is scaled-up, the majority of operating parameters would stay the same as found at bench-scale. The optimal range for parameters such as temperature, dissolved oxygen, and pH are scale independent. Among the scale dependent parameters are the mixing efficiency given by the impeller rate and aeration rate, and hydrostatic pressure. Agitation and aeration rates determine the quality of mixing, the gas–liquid mass transfer rates, and the hydrodynamic stress that the cells experience. Poor mixing can result in heterogeneities in pH, nutrient concentration and metabolic byproduct concentrations. In addition to the oxygen gas–liquid transfer rate, the carbon dioxide gas–liquid transfer rate should be taken into account. In the case of animal cells, carbon dioxide is a metabolic byproduct that can accumulate upto inhibitory levels unless adequate ventilation is provided (15,39). Strategies to minimize gas sparging (to reduce sparging-induced cell damage) can inadvertently result in accumulation of carbon dioxide (40,41).

The basic problem in scaling-up a stirred tank bioreactor used in animal cell cultivation is that at larger scales, quality of mixing, gas–liquid mass transfer rates, and hydrodynamic stress to the cells cannot all be kept identical to conditions at bench-scale. An impeller rate and sparge rate must be chosen that provides adequate mixing and gas–liquid mass transfer rates but minimizes cell damage due to shear stress. Animal cells are especially sensitive to mechanical stress as they lack the protective cell wall of bacteria and fungi. Although many correlations have been described for quality of mixing, gas–liquid mass transfer rates, and hydrodynamic stress, they should be used as guidelines rather than a predictor of bioreactor performance at large-scale. They will rarely predict accurately the properties of a bioreactor system under real operating conditions. For example, measurements of glucose and lactate in a murine hybridoma culture showed a shift toward anabolic metabolism at the 200 L scale that was not observed at the 3 L scale. This observation indicated that oxygen limitation was present at the larger scale, even using the constant impeller tip speed as a scale-up criteria. This problem could be obviated by, for instance, increasing the agitation rate at production scale or the set point for dissolved oxygen tension (22).

Quality of mixing is usually described in terms of a mixing (or circulation) time. Mixing times are generally determined by injecting a tracer into a

bioreactor and monitoring the signal until it decays to a predetermined level (for example, 99% of the final value). The simplest tracer is either acid or base with pH probes to monitor pH fluctuations. As bioreactor volumes increase, mixing times for equivalent impeller tip speeds inevitably increase. For instance, calculations of the theoretical mixing time in a 10 L bioreactor and a 10,000 L bioreactor, under typical operating conditions, show that this parameter can increase by an order of magnitude (42).

Aeration of stirred tank bioreactors can be accomplished by several methods, including direct sparging of gas through the culture, surface aeration, and silicon tubing aeration. Of these possibilities, direct sparging is the simplest method for supplying a production bioreactor with oxygen. The most commonly used parameter to quantify the gas transfer efficiency is the mass transfer coefficient expressed in terms of the total transfer area, or $k_L a$. Correlations for oxygen mass transfer rates based upon tank and impeller geometry can be found in many sources (9,39). However, it may not always be possible to find a correlation for a specific reactor configuration, i.e., geometry, impeller types, number of impellers, etc. Therefore, these correlations should be used as a rough estimation of the power input required to reach a certain gas transfer efficiency. Gas sparging has also been implicated in damaging animal cells (17). The high velocity gradients that develop around bursting bubbles can generate enough mechanical stress to damage animal cells. Addition of surfactants to the culture medium, such as Pluronic F68^{TM}, may prevent the attachment of cell to rising bubbles, reducing their exposure to shear stress (16).

The impact of hydrodynamic stress on animal cells has been reviewed extensively (29,43). Most of the work reported in the literature on cell damage in agitated bioreactors has been done at bench-scale. Kunas and Papoutsakis (44) reported that in 1–2 L bioreactors equipped with a 7 cm diameter pitched-blade impeller, cell damage was not observed until the impeller rate was raised to above 700 rpm (tip speed: 513 cm/s), as long as air entrapment did not occur. However, it is not clear how these bench-scale observations translate into damaging impeller rates at manufacturing scale.

Air-Lift Bioreactors

Fundamentally, air-lift bioreactors are a modification of the bubble columns that generate air-flow for medium circulation unidirectionally by having at least two columns—a raiser column and a downer column. They are either a draft tube or an external loop bioreactor. The bubbles sparged into a draft tube generate upward flow and medium pours into the annular space between the draft tube and bioreactor vessel and flows downwards. An essential design feature to consider is the bioreactor ratio of the height (H) to the diameter (D). Values of H/D of five or more are needed for sufficient mixing (18). Efficiency of medium circulation depends on the rate of aeration and on the ratio of the cross-sectional area of the draft tube to the total

cross sectional area of the bioreactor vessel. Air-lift bioreactors are superior for product yield and biomass production when applied to cells that are susceptible to shear under turbulence. Cell breakage caused by mechanical stirring could be minimized by the gentler mixing that air-lift bioreactors offer. Bacteria, yeast, plant, and animal cell cultures have been cultivated in these systems. Not only the simplicity of construction and maintenance but also an approximately 50% reduction in the power requirements makes them more attractive, due to operating cost reductions.

Mode of Operation of Bioreactors

The mode of operation of the bioreactors previously described can be largely classified as batch or continuous. The advantages or disadvantages of using either method are still the subject of controversy as proponents and detractors for each method are always well prepared to defend their positions.

Batch cultivation is perhaps the simplest way to operate a fermentor or bioreactor. It is easy to scale-up, easy to operate, and it offers a quick turn around and a reliable performance. Batch sizes of 15,000 L have been reported for animal cell cultivation (4) and vessels of over 100,000 L for fermentation are also available. Continuous processes offer the advantage of minimizing the "down time" of the production units, and homogeneity of product quality throughout the production cycle as cells are kept in a physiological steady state. Continuous processes can be classified into cell retention and non-cell retention. The devices typically used for cell retention are spin filters, hollow fibers, and decanters. Large-scale operation of continuous processes can reach up to 2000 L of bioreactor working volume. Typically, the process is operated at one to two bioreactor-volumes exchanged per day. Perfusion is one variation of a continuous process in which cells are retained within the bioreactor to achieve the highest level of product expression possible (45). Usually, high productivity in cell culture is achieved by a high specific productivity and/or high cell density. The major limitation of a batch is the accumulation of toxic metabolites and the depletion of nutrients. This is resolved in continuous systems such as perfusion where spent medium is continuously removed from the culture vessel and it is replaced by fresh medium. It is claimed that this method sustains high productivity for months of continuous operation (46).

The main disadvantage of a continuous system is the long time required for validation and timely submission of product application to the appropriate regulatory agency. This timeline is drastically reduced with the use of a batch system of equivalent volumetric productivity.

Harvest Operation

Biotechnology products synthesized by living cells are either contained within the cells (intracellular) or are secreted by the cells into the liquid broth

(extracellular). A clarification step is employed to remove the cells and debris before the purification process is initiated. Typical unit operations available for performing the clarification step include tangential-flow filtration (5,22,47), dead-end filtration (48), and centrifugation (49). Tangential-flow filtration is the most extensively used method because it minimizes cell damage and maximizes effective membrane surface use, flux, and membrane lifetime. It is readily scalable and can provide high processing rates with good efficiency without adversely affecting the cell viability. Critical operating parameters for optimizing the filtration condition are trans-membrane pressure, retentive-flow rate, and permeate flux. High shear conditions should be avoided to minimize cell rupture that leads to increased levels of contaminating cellular proteins and nucleic acids. The resulting increase in cell debris under such conditions also reduces the capacity of downstream sterile filters. Conventional dead-end filters are designed for sterile filtration of relatively clean fluids. The high amount of cells and debris in a typical cell culture broth makes the dead-end filtration approach impractical in terms of equipment size and filtration cost. A viable alternative is the use of depth filters that typically have graded porosity allowing substantially higher processing capacities. An in-line sterile filtration step is then used to eliminate the debris. Both batch and continuous centrifugation offer scalable high processing rates. The disadvantages include higher equipment and maintenance costs. Typically, the clarification efficiency of centrifugation is lower than that of the filtration operations because of the lower resolution of particle densities compared to size differences. This leads to an increased burden for downstream sterile filtration and additional efforts to remove process contaminants, such as DNA.

DOWNSTREAM OPERATIONS

Design of Purification Processes

From the many options available for purification, process design should be based on selecting among the multiple unit operations that maximize ease of purification, product purity and overall yield. In general, a simple stepwise purification design utilizing orthogonal methods of purification with maximum compatibility between steps is preferred. The use of orthogonal purification techniques is important for the removal of process contaminants to trace levels and for robust viral clearance. The number of product manipulations as well as the quantities and number of buffers, can be minimized by maximizing the compatibility of process steps. This consideration should be exercised early in the development of the process as it may have a huge impact later on buffer handling operations at large-scale. Initial steps using highly selective capture chromatography facilitate volume reduction and effective removal of the most problematic process contaminants. Effective intermediate and final polishing steps are necessary for the removal of

process contaminants to trace levels and virus inactivation and/or removal. The formulation step is designed to produce the final bulk dosage form of the product with appropriate concentration and long-term product stability. Careful and effective optimization for all process steps is essential for successful scale-up to manufacturing.

For purification, scale-up considerations are important even in the earliest phases of development. It is important to avoid the use of purification techniques of limited scale-up potential even for early clinical production because thorough justification of process changes and demonstration of biochemical comparability are necessary prior to product licensure. For successful scale-up, it is important to understand the critical parameters affecting the performance of each purification step at each scale. Conversely, it is important to verify that the scaled-down process is an accurate representation of the scaled-up process, so that process validation studies, such as viral clearance and column lifetime studies, can be performed at the laboratory scale.

Tables 2 and 3 show an antibody purification process scale-up from laboratory scale (1 mL) to intermediate scale (500 mL) to large scale of 10–85 L column volumes, maintaining the column bed height constant. Product quality and biocontaminant levels were maintained throughout the scale-up, though operational flow rates were significantly changed, demonstrating the consistency of the overall purification process. Thorough analysis of each column performance is essential in order to sustain the process robustness at different scales of operation.

Chromatography

The majority of the processes currently used to manufacture biotechnology products employ chromatography columns as the main tool for effective product recovery and purification. The scale-up (50) and validation (51) of this vastly popular unit operation are the keys for successful implementation

Table 2 Antibody Purification Process Scale-Up and Performance for Different Bioreactor Scales

	5000 L Scale			350 L Scale		
Process parameter	1[a]	2	3	1	2	3
Column size						
Diameter (cm)	63	80	63	30	30	30
Height (cm)	16.0	17.0	16.5	15.5	14	15.5
Resin volume (L)	49.9	85.4	51.4	10.95	9.89	10.95
Linear flow rate (cm/hr)						
Operational	154	150	150	272–450	150	300

[a]Column number.

Table 3 Recovery and Product Quality at Different Scales of Purification Process

Product quality and recovery	5000 L Bioreactor scale			350 L Bioreactor scale		
	1[a]	2	3	1	2	3
Contaminant levels						
HCP (ng/mg)	957	38	4	813	24	2.3
DNA (pg/mg)	204	2	0.5	11.4	15.3	0.3
Purity						
Monomer (%)	100	100	100	100	100	100
HPLC SEC						
Recovery (%)	81	94	96	90	97	96

[a]Column number.

of the overall production strategy at large-scale and eventual product approval for commercialization.

If an ion exchange step is to be used as an initial capture chromatography step, pH or conductivity adjustment of the conditioned medium might be necessary. At large-scale, conductivity adjustment can be accomplished by in-line dilution without increasing the number or volume of the vessels required. Some manufacturers carry out a concentration and/or diafiltration for buffer exchange and volume reduction prior to the capture chromatography step. In this case, whatever time and effort is saved in loading the initial capture chromatography must be weighed against the time for the concentration/diafiltration, and the time for cleaning and preparation of ultra filtration cartridges, as well as additional buffer preparation time.

Many manufacturers prefer to use an initial capture affinity chromatography step. The affinity gels are highly selective and generally require little or no manipulation of a feed stream. Some possible disadvantages of using an initial affinity column step are the expense of the affinity matrix and the fact that repetitive exposure of the matrix to conditioned medium may require stringent cleaning procedures, which may reduce the effective lifetime of the gel. The cost issue can be obviated somewhat by using smaller columns and multiple cycles. However, this will extend processing time and increase labor cost. For subsequent chromatography steps, ion exchange frequently may follow or precede HIC. HIC product is often eluted at low salt concentrations, which is compatible with the low conductivity necessary for binding to ion exchange gels. Conversely, an ion exchange product is often eluted at high salt conditions, which may provide conditions compatible with HIC chromatography.

Viral Clearance

Viral inactivation and/or removal steps are a critical part of the process design for biotechnology products derived from mammalian cell culture

systems. Regulatory agencies are concerned with the presence of endogenous and/or adventitious agents in the cell lines an/or raw materials employed to manufacture pharmaceutical proteins from cell culture (52). The best approach to ensure adequate viral clearance is to have multiple orthogonal virus removal steps and at least one viral inactivation step. Viral removal, demonstrated with spiking studies using model viruses, should be carried out with a scaled-down version of the purification process, which accurately represents the process used at manufacturing scale. In addition, it is recommended that studies include the use of typical critical operating parameters for each step, as well as conditions that represent a worst case for viral removal. For instance, for process validation of chromatography steps, extremes of linear velocity, protein concentration, reduced bed height or contact time, and total protein capacity should be tested. Although it is often difficult to adequately quantitate viruses in various column fractions, it is important, whenever possible, to characterize viral removal in the product fraction as well as in the non-bound flow through wash and strip fractions. Viral inactivation steps, using chemical or physical conditions such as low pH, heat, irradiation, or chemical agents, should be characterized by performing kinetic inactivation studies. For these studies, typical and worst case conditions should be evaluated. For example, if a product is eluted with a low pH buffer, a manufacturer might consider holding the product at the low pH as the viral inactivation step. However, because the product has some inherent buffering capacity, the final pH value of the eluted product may change based on the protein concentration or, as the process is scaled-up, the eluted product pH may shift slightly due to subtle modifications in the collected product peak. The low pH tested in viral inactivation studies must be based on the maximum eluted product pH, which may not be known prior to scale-up. For these reasons, it may be preferable to define a separate inactivation step in a single vessel with sub-surface addition and mixing of the inactivating agent to provide precise control of the hold time, temperature, and pH.

PROCESS CONTROLS

Adequate monitoring of the process can ensure proper and successful operation of the process at any scale. The design and logical integration of process-associated analytical testing has gained importance in the monitoring and controlling of bioprocess. This technique has culminated in the introduction of the PAT (Process Analytical Technologies) initiative for biologics by regulatory agencies as previously applied in pharmaceutical processing. As a result, adequate testing of process performance and product quality at relevant process steps can be implemented to ensure process robustness and ultimately lead to lot-to-lot consistency. Identification of relevant analytical technique(s) and critical process steps could be done at the process

development stage, which could later be integrated into the manufacturing process and could be effectively utilized in the process characterization and validation stages. The ultimate goal is to rely on process monitoring to reduce lot-to-lot testing, expedite lot release, and even to eliminate the need for process validation.

SCALE-DOWN MODELS

The development of scale-down models for various process steps plays a significant role in predicting the outcome of the process at the manufacturing scale. An example of a well-accepted use of the scale-down model in the manufacturing of biologics is conducting viral removal and inactivation studies as part of the protein purification scheme. Similarly, a well designed scale-down model can serve as a basis for setting the ranges for process critical parameters that are essential for consistent performance of process to yield the desirable product, which achieves its quality attributes. At the same time, these models can also predict the conditions that can lead to failure of process performance and can set the stage for process validation at manufacturing scale. The recent introduction of small multiple-mini bioreactors set ups (53) makes it possible to conduct experiments by statistical design using multiple and simultaneous cell culture conditions. Also, feed composition development is facilitated, by using these multi-unit devices. This type of arrangements, tied to high-throughput data acquisition and analysis software, is becoming a more widely used tool to minimize cell culture development time and costs.

FACILITY DESIGN

Facility design is also an important consideration in process design and scale-up. An important observation to be made up-front is that the market size for biologics bears little correlation with the size or volume of production (Table 4).

Therefore, the scale-up for biologics does not necessarily result in a decision to build a new facility or to design large-scale equipment. It is largely dependent on the product's intrinsic nature, potency, and demand.

Another special feature of biologics is that facilities are usually designed for a specific product in mind, with little room for flexibility to match the process developed for alternative products in the pipeline. This is the opposite case from that found in the manufacture of small drug pharmaceuticals where unit operations, lay out, and equipment can be used for multiple products. This makes the decision even more challenging to build a manufacturing facility for biologics.

Retrofitting an existing facility for commercial manufacture can be costly. Sometimes the constraints imposed by an existing plant have to be considered in the design of a process. In this case, it is helpful to create a

Table 4 Market Size for Selected Biologics

Product	Marketed in the US by	Estimated demand (kg) (2001) (Ref. 54)	Estimated demand (US $) (2001) (Ref. 54)	Actual demand (US $) (2003)
Enbrel	Amgen	200	1.1 B	1.3 B
Remicade	J&J	110	0.8 B	1.7 B
Rituxan	IDEC-Biogen/Genentech	220	1.1 B	1.35 B
Herceptin	Genentech	100	0.6 B	0.43 B
Synagis	MedImmune	20	0.3 B	0.85 B
Epogen	Amgen	2	1.3 B	2.4 B

Abbreviation: B, billion.

spreadsheet template for scale-up calculations to test and evaluate the operation of the process in an existing environment with minimal changes to existing equipment. Examples of such calculations are found for buffer preparation, bioreactor and harvest operations, filtration operations, product and buffer tanks, chromatography controllers, hard piping, and flow patterns. For example, if existing product tanks are too small, chromatography column sizes can be reduced and multiple cycles need to be performed. However, the long-term costs associated with smaller chromatography columns and extended processing times must be weighed against the initial costs of purchasing and installing larger vessels or columns. The operational segregation of pre- and postviral clearance steps may also require re-design of a facility and should be considered in the early stages of process development. However, the advent of new technologies using self-contained unit operations and disposable systems (19) may actually change the current philosophy of facility layout in the near future.

EXAMPLES OF PROCESS SCALE-UP

Once process design is complete and each of the process steps is characterized, the process is ready for scale-up to pilot or manufacturing scale. A spreadsheet template for scale-up calculations is important and provides a mass balance of buffer volumes, column volumes, priming volumes, product volumes, and waste volumes, as well as tank size and column size. Product volumes can be expressed relative to column volume or can be calculated from a constant concentration, depending on the process step. In addition, starting volumes and titers of conditioned medium, as well as step yields and gel or membrane capacity, are necessary to calculate bed volumes and membrane surface area for the purification steps. A worst-case approach assuming maximum step yields, product volume, and starting titer is recommended, except for cases where underloading a column or a membrane step is problematic.

Some general observations were made during the scale-up of a process using microfiltration operations at the bioreactor stage (25). One was that when using tangential flow filtration, the ratio between retentive flow and permeate flow has to be at least five to one in order to avoid the effect known as "dead-end filtration." This finding clearly indicated the need for an additional control on the permeate flow which was not necessary in the small-scale experiments. Another observation was that the ratio of filtration area (FA) to process volume (PV) usually employed as a rule for scale-up may actually decrease as the scale of operation increases. This is due to a more efficient utilization of the membrane surface with the consequent savings in filtration equipment.

It is also important to recognize the interaction between the scaling parameters. Simply multiplying an existing process by the next scale-up factor may lead to errors. For example, if a single 10-in. filter is used at 66% capacity in the pilot scale, a four-fold increase in scale does not require four 10 in. filters. Rather, three 10 in. filters or a single 30-in. filter can be used at 88% capacity.

Another example demonstrating the interaction between scaling factors comes from chromatography operation. As the process scale increases, the available column volume must increase, either by packing larger columns or by running multiple cycles. Columns are generally available with 30, 45, 60, 100 and 200 cm diameters. The selected column diameter is the result of calculating a required gel volume considering both minimum bed height resin and dynamic capacity. It is necessary to select a column diameter when doing calculations and then determine the resulting bed height based on the required volume. Using a narrower diameter column will result in increased processing time because, generally, the linear velocity is held constant during scale-up. The alternative is to use a shorter, wider column, but there is a minimum bed height that can be used at large scales, generally $\geq$10 cm. The use of a larger diameter column will increase flow rate and decrease operating time. However, the use of a wider column may necessitate packing a column of larger volume than necessary from the given gel capacity. The larger volume column means that greater volumes of buffer are needed and that product volumes will likely increase. It is important to determine if tanks are available for the additional volumes of product and buffers. In this example (Table 5), as the effective (dynamic) gel (resin) capacity decreases, the processing time decreases and the buffer volumes increase.

For buffer exchange or formulation steps using ultra filtration, membrane capacity and processing time are closely linked. In contrast with the previous example focusing on chromatography capacity, as membrane capacity decreases, there is no dramatic increase in buffer usage. In general, decreasing the membrane capacity reduces processing time because the gel layer is thinner and has less impact on permeated flux. However, as the membrane surface area increases, a larger size ultra filtration system is required and larger pumps are required to maintain the recirculation flux.

Table 5 Sample Scale-Up Calculation for a Chromatography Step

Assumptions		Units				
Titer	0.5	g/L				
Harvest volume	2000	L				
Total product	1000	g				
Maximum gel capacity	20.0	g/L gel				
Minimum gel volume	50	L				
Minimum bed height	10.0	cm				
Linear velocity	300	cm/hr				
	Case 1			Case 2		
Column diameter (cm)	60			100		
Calculated bed height (cm)	17.7			6.4		
Actual bed height (cm)	17.7			10.0		
Actual column volume (L)	50			79		
Actual capacity used (g/L gel)	20.0			12.7		
Flow rate (L/min)	14.1			39.3		
Operation	Solution usage (L/L)	Solution volume (L)	Duration (min)	Solution usage (L/L)	Solution volume (L)	Duration (min)
Equilibration	5	250	17.7	5	393	10.0
Load		2000	141.5		2000	50.9
Post-load equilibration	3	150	10.6	3	236	6.0
Wash	5	250	17.7	5	393	10.0
Elution	6	300	21.2	6	471	12.0
Sanitization	3	150	10.6	3	236	6.0
Storage	3	150	10.6	3	236	6.0
Grand Totals		3250	229.9		3964	100.9

For a highly concentrated product, a large system hold-up volume increases the potential for product loss. For concentration/diafiltration operations, scale-up may require re-optimization of process parameters, especially if membrane capacities are changed. However, every effort should be made to keep recirculation flux constant with similar inlet and outlet pressures.

IMPACT OF SCALE-UP ON PROCESS PERFORMANCE AND PRODUCT QUALITY

One of the chief concerns when scaling up biological process is the effect of minor variations in the microenvironment at different scales that may affect process yields and product quality.

Due to the complex nature of biologics, extensive biochemical characterization of physico–chemical parameters is needed to demonstrate product comparability upon scale-up. If any differences are detected, there is the possibility of having to perform animal and/or human studies to further demonstrate product comparability upon scale-up.

There is so much concern about this issue that in some instances in the past, it has been considered preferable to increase the number of units instead of the scale of each unit of production to avoid potential differences in product quality. In some other instances, an approved biologic, even thought manufactured using less than ideal methods, may not be deemed to be replaced by a more advanced manufacturing method due to differences in the protein structure or composition. The market value of biologics and their complexity justifies this ultra conservative approach.

Nowadays, however, the analytical tools and the cummulative regulatory experience available make it possible to propose upgrades of production methods to either preapproved or to already approved products. In order for these changes to be implemented, the sponsor needs to demonstrate that the product is comparable before and after the changes.

An example of a typical panel of tests performed on monoclonal antibodies to demonstrate comparability is shown in Table 6.

Glycosylation of proteins has taken the lion's share of attention among different post-translational modifications that are essential for maintaining the efficacy and, pharmacokinetics of several therapeutic proteins. Carbohydrate profiles are subjected to changes with elevated expression levels and, in some cases, scale of bioreactor runs. Monitoring this parameter from early on while choosing the cell line for various stages of process development, including selection of basal and feed media and during scale-up of the process, will ensure the product quality. Different innovative technologies to achieve desirable glycosylation of proteins have been employed. To circumvent the differences that arise from variations in glycosylation, expression hosts such as yeast can be genetically engineered to perform glycosylation reactions similar to those in humans (12). Another approach is to engineer CHO cell lines

Table 6 Typical Assays Used in the Comparability Testing of Monoclonal Antibodies

Protein chemistry	Carbohydrate chemistry
Size exclusion HPLC	*N*-Glycan profile
SDS-PAGE (reduced and non-reduced)	*N-Glycan mapping*
Western blots	Monosaccharide composition
Isoelectric focusing (IEF)	Sialic acid content
Capillary IEF (c-IEF)	*N*-Glycan structure and population
C-Terminal lysine variants	*N*-Glycosylation site
C-Terminal sequence of heavy chain	
N-Terminal sequence of heavy and light chains	Functional assays
Molecular weight of heavy and light chains	• Binding (e.g., ELISA, BiaCore, etc)
Peptide mapping	• Potency (e.g., cell based, ELISA)
Amino acid analysis	
Intrinsic fluorescence spectroscopy	
Thermal denaturation monitored by fluorescence	
Fourier transfrome infrared spectroscopy	

that are deficient in a specific sugar moiety addition. An example of this approach is the development of mutant CHO cells incapable of adding fucose to recombinant antibodies. Fucose-deficient antibodies have been shown to increase ADCC activity in vitro, which in turn may lead to a decrease in the dose of antibodies requiring effector's functions in vivo (55,56). Recently, an alternative human cell line known as Per.C6, a human transformed retinoblast cell line, is being proposed as a high yield production system for recombinant proteins requiring human glycosylation. This cell line can be grown in standard bioreactors and using standard cell culture techniques to 100×10^6 cells/mL in perfusion cultures and has also been reported to be able to produce over 2.5 g/L in fed-batch cultures (11).

SUMMARY

Once the scale-up factors have been established, the scale-up of the process from pilot to manufacturing scale should be relatively straightforward. There are, of course, important considerations for working in a commercial manufacturing environment that have not been addressed in this chapter.

These include, but are not limited to, cGMP and regulatory compliance issues such as the need to provide proper segregation of pre- and post-viral clearance steps, ensure uni-directional flow of material and personnel, cleaning of the facility, waste handling, and environmental monitoring of the facility (37,57). In order to scale-up and transfer a process successfully from laboratory scale to pilot scale and multiple commercial manufacturing scales,

a thorough understanding of the integration of scale factors, facility design, equipment design, and process performance is necessary. A scale-up template spreadsheet can be a useful tool to provide the critical integration of multiple factors. Ultimately, the ability to produce a product with the desired quality attributes is demonstrated during process validation. This is an absolute requirement to obtain market authorisation for a biological.

FINAL REMARKS AND TECHNOLOGY OUTLOOK

The entire field of biotechnology includes not only cell culture-derived biologics, but also transgenic systems (animals, plants, and insects), and more recently, the revival of traditional fermentation using yeasts and fungi. The combined efforts in these areas over the last five years have resulted in an astounding improvement of manufacturing yields. Product titers as high as 7 g/L in cell culture of CHO cells (58) are becoming more common. Many are predicting product titers of close to 7–10 g/L as the norm in the next three to five years, which could be easily inferred from the existing data, using low and high estimates (Fig. 5).

The immediate effect of these improvements in product yield is a dramatic decrease in the cost of manufacturing. However, it also means that in order to match this performance, recovery and purification operations

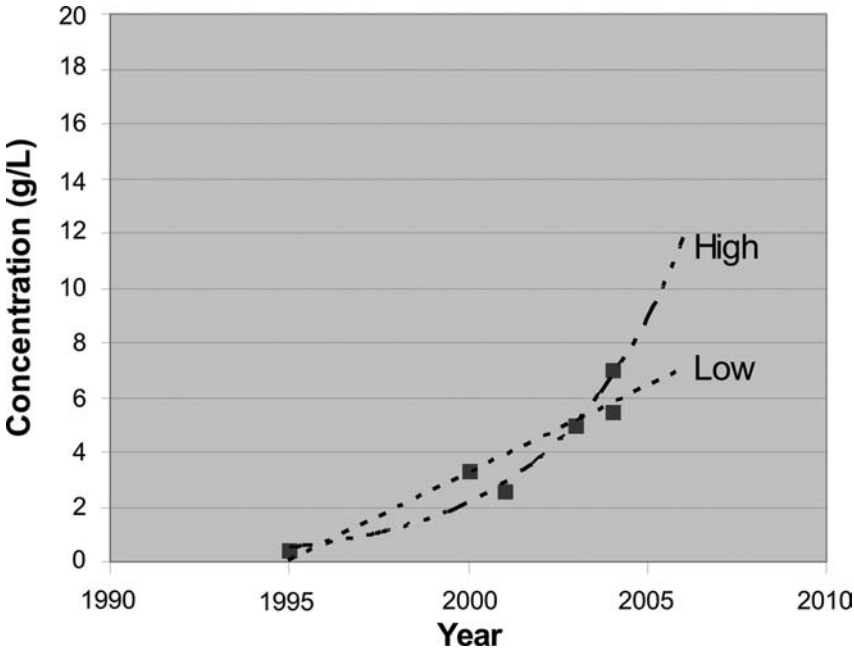

Figure 5 Projections for antibody concentrations obtained from cell culture.

need to improve. Further development of resins having dynamic capacities of over 100 mg/mL is needed to absorb this increased throughput from upstream and the equipment necessary to operate chromatography columns at high flow rates. The development of filter-based separation of proteins using charged membranes offers an alternative to chromatography-based processes for very high throughput conditions. Also, the knowledge gathered during formulation development work should be incorporated to purification activities such as in-process hold times and handling of final product solutions at high concentrations in order to reduce the size of storage tanks and containers, minimizing capital investment in equipment requirements and facility design. The future challenges for antibody production using cell culture technologies are to achieve the "3×100s" goal: 100 pg/cell/day for specific productivity, 100×10^6 cells/mL of viable cell density, and 100 mg/mL of dynamic resin capacity in the near future. These challenges are already being met, although separately. For instance, a cell density of 100×10^6 cells/mL using PER.C6 cells has been reported in perfusion (59,60), and 100 pg/cell/day using the GS expression vector is possible (61). Further modifications in the structure and composition of protein therapeutics could conceivably yield more potent proteins (62), thereby decreasing dose size and scale of manufacturing.

The use of Process Analytical Technology (PAT) to fully characterize and control the manufacturing process may enable the biotechnology industry in the not too distant future to produce these complex molecules as cheaply and efficiently as traditional small molecule drugs.

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6

Batch Size Increase in Dry Blending and Mixing

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BACKGROUND

In the manufacture of many pharmaceutical products (especially tablets and capsules), dry particle blending is often a critical step that has a direct impact on content uniformity. Tumbling blenders remain the most common means for mixing granular constituents in the pharmaceutical industry. Tumbling blenders are hollow containers attached to a rotating shaft; the vessel is partially loaded with the materials to be mixed and rotated for some number of revolutions. The major advantages of tumbling blenders are large capacities, low shear stresses, and ease of cleaning. These blenders come in a wide variety of geometries and sizes, from laboratory scale [$<$16 quart (qt.)] to full size production models ($>$500 ft^3). A sampling of common tumbling blender geometries includes the V-blender (also called the twin-shell blender), the double cone, the in-bin blender, and the rotating cylinder.

There are currently no mathematical techniques to predict blending behavior of granular components without prior experimental work. Therefore, blending studies start with a small scale, try-it-and-see approach. The first portion of this chapter is concerned with the following typical problem: a 5-ft^3- capacity tumble blender filled to 50% of capacity and run at 15 rpm for 15 minutes produces the desired mixture homogeneity. What conditions

should be used to duplicate these results in a 25-ft^3 blender? The following questions might arise:

1. What rotation rate should be used?
2. Should filling level be the same?
3. How long should the blender be operated?
4. Are variations to the blender geometry between scales acceptable?

Unfortunately, there is no generally accepted method for approaching this problem; therefore, ad hoc approaches tend to be the rule rather than the exception.

Further complicating the issue is that rotation rates for typical commercially available equipment are often fixed, obviating question (1) and suggesting that, under such conditions, true dynamic or kinematic scale-up may not be possible.

GENERAL MIXING GUIDELINES

Defining Mixedness

Before specifically addressing scale-up of tumbling blenders, this section discusses some general guidelines that cover the current understanding of the important issues in granular blending. The final objective of any granular mixing process is to produce a homogenous blend. But even determining mixture composition throughout the blend is a difficulty for granular systems. As yet, no reliable techniques for on-line measuring of composition have been developed; hence, granular mixtures are usually quantified by removing samples from the mixture. To determine blending behavior over time, the blender is stopped at fixed intervals for sampling; the process of interrupting the blend cycle and repeated sampling may change the state of the blend. Once samples have been collected, the mean value and sample variance are determined and then often used in a mixing index. Many mixing indices are available; however, there is no "general mixing index," so the choice of index is left to the individual investigator (1). Once a measure of mixedness has been defined, it is then tracked over time until suitable homogeneity is achieved. Ideally, this minimum level of variance would stay relatively constant over a sufficiently long window of time. This procedure is simple in concept, but many problems have been associated with characterization of granular mixtures (2).

One dangerous assumption is that a small number of samples can sufficiently characterize variability throughout the blend. Furthermore, sample size can have a large impact on apparent variability. Samples that are too small can show exaggerated variation, while too large a sample can blur concentration gradients. Unlike miscible fluids, which, through the action of diffusion, are continually mixing on a microscale, granular blends only mix when energy is

inputted into the system. Hence it is paramount that a sufficient number of samples is taken that represents a large cross-section of the blender volume.

Another concern is thinking that standard sampling techniques retrieve samples that are truly representative of local concentration at a given location. Thief probes remain the most commonly employed instrument for data gathering. These instruments have been demonstrated to induce sometimes large sampling errors as a result of poor flow into the thief cavity or sample contamination (carryover from other zones of the blender) during thief insertion (2). Care and skepticism have to be employed whenever relying on thief probes data. One method to assess blend uniformity and blend sampling error is given in PDA Technical Report No. 25 (3).

Finally, the degree of mixedness at the end of a blending step is not always a good indicator of the homogeneity to be expected in the final product. Many granular mixtures can spontaneously segregate into regions of unlike composition when perturbed by flow, vibration, shear, etc. Once a good blend is achieved, the mixture still must be handled carefully to avoid any "de-mixing" that might occur. The second half of this chapter deals with the scaling of flow from blenders, bins and hoppers, and the effect of segregation during handling.

Mixing Issues in Tumbling Blenders

Mixing in tumbling blenders takes place as the result of particle motions in a thin cascading layer at the surface of the material, while the remainder of the material below rotates with the vessel as a rigid body. Current thinking describes the blending process as taking place by three essentially independent mechanisms: convection, dispersion, and shear. Convection causes large groups of particles to move in the direction of flow (orthogonal to the axis of rotation) as a result of vessel rotation.

Dispersion is the random motion of particles as a result of collisions or interparticle motion, usually orthogonal to the direction of flow (parallel to the axis of rotation). Shear separates particles that have joined due to agglomeration or cohesion and requires high forces. While all mechanisms are active to some extent in any blender, tumbling blenders impart very little shear, unless an intensifier bar (I-bar) or chopper blade is used (in some cases, high shear is detrimental to the active ingredient, and is avoided). While these definitions are helpful from a conceptual standpoint, blending does not take place as merely three independent scaleable mechanisms. However, attentive planning of the blending operation can emphasize or de-emphasize specific mechanisms and have significant impact on mixing rate.

Most tumbling blenders are symmetrical in design; this symmetry can be the greatest impediment to achieving a homogeneous mixture. The mixing rate often becomes limited by the amount of material that can cross from one side of the symmetry plane to the other (4–8). Some blender types have been built asymmetrically (e.g., the slant cone, the offset V-blender), and show

greater mixing proficiency. Furthermore, by rocking the vessel as it rotates, the mixing rate can also be dramatically increased (9). Asymmetry can be "induced" through intelligent placement of baffles, and this approach has been successfully tested on small-scale equipment (7,10–12) and used in the design of some commercial equipment. But, when equipment is symmetrical and baffles unavailable, careful attention should be paid to the loading procedure as this can have an enormous impact on mixing rate.

Non-systematic loading of multiple ingredients will have a dramatic effect on mixing rate if dispersion is the critical blending mechanism. For instance, in a V-blender, it is preferable to load the vessel either through the exit valve or equally into each shell. This ensures that there are nearly equal amounts of all constituents in each shell of the blender. Care must be taken when loading a minor ($\sim$1%) component into the blender—adding a small amount early in the loading process could accidentally send most of the material into one shell of the blender and substantially slow the mixing process. Smaller blenders entail shorter dispersal distances necessary for complete homogeneity, and thus may not be as affected by highly asymmetrical loading. As a final caution, the order of constituent addition can also have significant effects on the degree of final homogeneity, especially if ordered mixing (bonding of one component to another) can occur within the blend (13).

Intershell flow is the slowest step in a V-blender because it is dispersive in nature while intrashell flow is convective. Both processes can be described by similar mathematics, typically using an equation such as

$$\sigma^2 = Ae^{-kN} \tag{1}$$

where σ^2 is the mixture variance, N the number of revolutions, A an unspecified constant, and k is the rate constant (6,14). The rate constants for convective mixing, however, are orders of magnitude greater than for dispersive mixing. Thus, unequal loading across the symmetry plane places emphasis on dispersive mixing and is comparatively slow compared to top-to-bottom loading, which favors convective mixing.

Process Parameters

When discussing tumbling blender scale-up, one parameter consideration that arises is whether rotation rate should change with variations in size. Previous studies on laboratory scale V-blenders and double cones have shown that, when far from the critical speed of the blender, the rotation rate does not have strong effects on the mixing rate (6,7) (the critical speed is the speed at which tangential acceleration due to rotation matches the acceleration due to gravity). These same studies showed that the number of revolutions was the most important parameter governing the mixing rate. An equation was derived by assuming that the mixture went through a specific incremental increase in mixedness with each revolution (either by dispersion or convection). While this approach has

been shown to be successful at modeling increasing in-mixture homogeneity, no scaling rules have been determined for the rate constants that govern this equation, and it remains an open question for further inquiry.

Given a geometrically similar blender and the same mixture composition, it would seem obvious that the fill level should also be kept constant with changes in scale. However, an increase in vessel size at the same fill level may correspond to a significant decrease in the relative volume of particles in the cascading layer compared to the bulk—this could accompany a large decrease in mixing rate. It has been shown in 1 pint v-blenders that running at 40% fill brings about a mixing rate that is nearly three times faster than at 60% fill (6). Thus, although fill level should be kept constant for geometric similarity, it may be impossible to match mixing rate per revolution across changes in scale if the depth of the flowing layer is a critical parameter.

SCALE-UP APPROACHES

In the literature, the Froude number ($Fr \equiv \Omega^2 R/g$; where Ω is the rotation rate, R the vessel radius, and g is the acceleration from gravity) is often suggested for tumbling blender scale-up (15–18). This relationship balances gravitational and inertial forces and can be derived from the general equations of motion for a general fluid. Unfortunately, no experimental data have been offered to support the validity of this approach. Continuum mechanics may offer other dimensionless groups if a relationship between powder flow and powder stress can be determined. However, *Fr* is derived from equations based on continuum mechanics, but the scale of the physical system for blending of granular materials is on the order of the mean free path of individual particles, which may invalidate the continuum hypothesis. A less commonly recommended scaling strategy is to match the tangential speed (wall speed) of the blender; however, this hypothesis also remains untested (Patterson–Kelley, personal communication, 2000).

We now look at our general problem of scaling the 5 ft^3 using *Fr* as the scaling parameter: the requisites are to ensure geometric similarity (i.e., all angles and ratios of lengths are kept constant), and keep the total number of revolutions constant. With geometric similarity, the 25 ft^3 blender must look like a photocopy enlargement of the 5 ft^3 blender. In this case, the linear increase is ($5^{1/3}$) or a 71% increase. Also, for geometrical similarity, the fill level must remain the same. To maintain the same *Fr*, since *R* has increased by 71%, the rpm (Ω) must be reduced by a factor of $(1.71)^{-1/2} = 0.76$, corresponding to 11.5 rpm. In practice, since most blends are not particularly sensitive to blend speed, and available blenders are often at a fixed speed, the speed closest to 11.5 rpm would be selected. If the initial blend times were 15 minutes at 15 rpm, the total revolutions of 225 must be maintained with the 25 ft^3 scale. Assuming 11.5 rpm were selected, this would amount to a 19.5-minute blend time. Although this approach is convenient and used often, it remains empirical.

Common violations of this approach that can immediately cause problems include the attempt to scale from one geometry to another (e.g., V-blender to in-bin blender), changing fill level without concern to its effect, and keeping blending time constant while changing blender speed.

The lack of first-principle, reliable scale-up criteria can have major impacts on development time and costs. Non-systematic means of scale-up can often lead to excessively long processing times and inefficient use of existing capacity. Long processing times can lead to unwanted side effects, such as particle sintering, heat build up, attrition, or excessive agglomeration. The advantages of rigorous scale-up include decreased process uncertainty, as we "know" what is going on. It also cuts down on the development time and experimental failures because experiments are done in a systemic manner that is based on science (not art).

NEW APPROACH TO THE SCALE-UP PROBLEM IN TUMBLING BLENDERS

Herein, we offer a first step toward the definition of rigorous scale-up rules for tumbling blenders. We begin by proposing a set of variables that may control the process. The driving force for flow in tumbling blenders is the acceleration from gravity, which must be included in our analysis. Vessel size is obviously a critical parameter, as is the rotation rate, which defines the energy input into the system. These variables define the system parameters (i.e., the driving forces) but do not cover the mixture response. In the case of Newtonian fluids, fluid viscosity connects the driving force (pressure gradients, gravity, and shear) to the fluid response (velocity gradients). For granular mixtures, no similar parameter has been derived; hence, we will define particle size and particle velocity as our "performance variables." Particle size plays a large role in determining mixing (or segregation) rates because dispersion distance is expected to vary inversely with particle size. For granular processes, individual particles drive bulk mixture behavior and we have assumed particle velocity to be an important variable. Because all transport and mixing phenomena are driven by the motions of individual particles, it is a priori impossible to scale transport phenomena without first scaling the velocities of individual particles. Although previous studies have indicated that rotation rate (and, hence, probably particle velocities) do not affect mixing rate, these experiments were done in very small blenders. It is conceivable that, at larger scales, these variables could become important. Given these assumptions, we can now address the development of non-dimensional scaling criteria.

Applying Rayleigh's Method

Our hypothesized set of the variables that are believed to govern particle dynamics in tumbling blenders is shown in Table 1.

Table 1 Variables Important to Scaling Particle Velocities in Cylinders

Variable	Symbol	Dimensions
Particle velocity	V	L/T
Vessel rotation rate	Ω	1/T
Vessel radius	R	L
Acceleration from gravity	g	L/T^2
Particle diameter	d	L

Abbreviations: L, length; T, time.

Using these variables and the Rayleigh method, the resulting equation is

$$V = k\Omega^a R^b d^c g^e \tag{2}$$

Applying the rule of dimensional homogeneity and making c and e the unrestricted constants leads to

$$V = k\Omega^{1-2e} R^{1-c-e} d^c g^e \tag{3}$$

To solve Equation (3), a correlation relating particle velocities to vessel radius and rotation rate is discussed in the following sections.

Correlating Particle Velocities to Vessel Rotation Rate and Radius

In order to determine particle velocities, an empirical approach is taken. A digital video camera was used to record the positions of individual particles on the flowing surface in clear acrylic, rotating cylinders of 6.3, 9.5, 14.5, and 24.8 cm diameter filled to 50% of capacity. Experiments were performed using nearly monodisperse 1.6-mm glass beads (Jaygo, Inc.) that are dyed for visualization. The displacement of particles from one frame to the next was converted into velocities. To calculate velocity, only the motion down the flowing layer was used, and all cross-stream (i.e., dispersive) motion was ignored. Figure 1 shows an example of the data obtained from a typical experiment. Top-to-bottom in the rotating cylinder is equivalent to left-to-right on this graph (Ref. 19 for details).

Figure 2 shows the mean cascading velocity versus distance down the granular cascade for experiments run at the same tangential velocity (TV). Despite a nearly fourfold difference in diameter, the velocity data all fall on nearly the same curve over the first 3 cm down the flowing layer. This agreement indicates that initial particle accelerations may be nearly equivalent, regardless of vessel size. Scatter in the experimental data shown in Figure 2

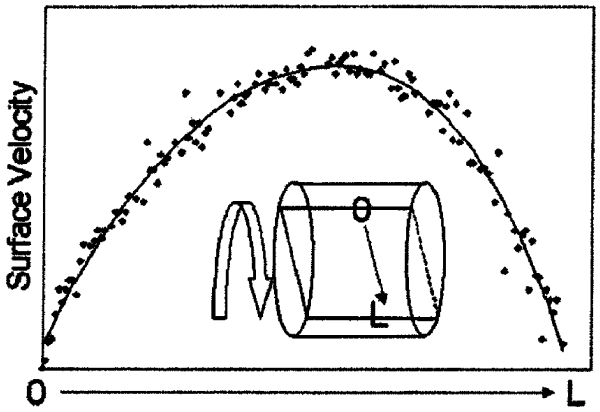

Figure 1 A typical velocity profile. Moving from top to bottom (0–L) in the rotating cylinder (inset) is equivalent to moving from left to right in the graph.

precludes direct calculation of accelerations, so least square polynomials were fit to the experimental data.

By differentiating the polynomial fit, we obtain an estimate of the downstream acceleration, shown in Figure 3. Over the initial or upper third (0–1/3 L) of the flowing layer, the acceleration profiles for all cylinders are nearly identical with only minor variations in magnitude. Although

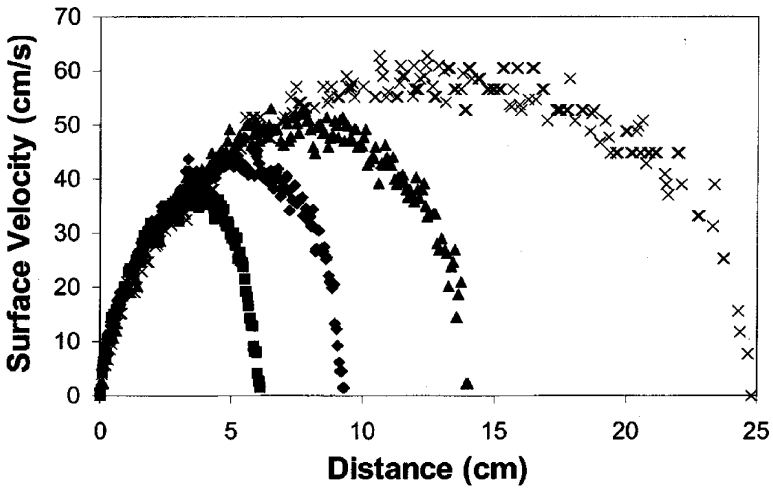

Figure 2 Velocity profiles for a series of experiments run at the same TV (26.4 cm/sec) in cylinders with inner diameters of 6.3 cm (■), 9.5 cm (◇), 14.4 cm (▲), and 24.8 cm (×), which correspond to rotation rates of 40, 26.5, 17.4, and 10.2 rpm, respectively.

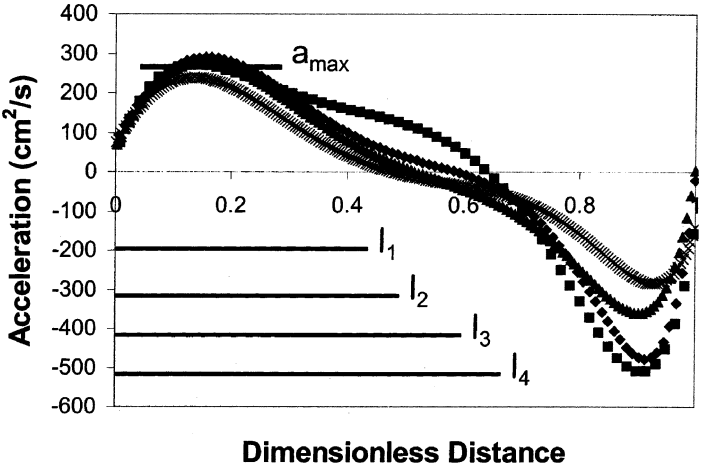

Figure 3 Acceleration profiles for experiments run at the same tangential velocity (13.2 cm/sec); l marks the distance to reach 0 acceleration. The velocity profiles are shown in Figure 2.

the qualitative trend is the same for all curves, the distance taken to reach zero acceleration is very different, nearly two-thirds of the vessel diameter in the 6.3 cm cylinder, as opposed to only half the diameter in the 24.8 cm cylinder.

In Figure 3, maximum accelerations are nearly equal, implying that TV may be proportional to maximum acceleration. Maximum accelerations were determined for all experiments; the results are plotted against the TV in Figure 4. An approximate linear fit is

$$a_{\max} = a \times \mathrm{TV} \tag{4}$$

where TV is the tangential velocity ($=2\pi R\Omega$) and $\alpha = 17/\mathrm{sec}$, is seen relating acceleration and TV for all cylinders and rotation rates. While the data clearly displays curvature, this linear fit is used as a first order approximation for scaling purposes.

In Figure 3, the distance to reach 0 acceleration varies greatly among the four different velocity profiles. This parameter, denoted l, is quantitatively measured as the distance at which the relative change in velocity drops below a preset limit. However, by itself, the value of l has little meaning; it is the parameter l/r, where r is the cylinder radius, that has a quantitative effect on the velocity profile and maximum velocities. When all values of l/r were compiled, a strong correlation to rotation rate was noted. As most pharmaceutical blenders are run at low rotation rates, we restrict the remaining discussion to vessel rotation rates below 30 rpm. Figure 5 plots l/r against $\sqrt[3]{\Omega}$, showing a nearly linear relationship below $\sim$30 rpm. An

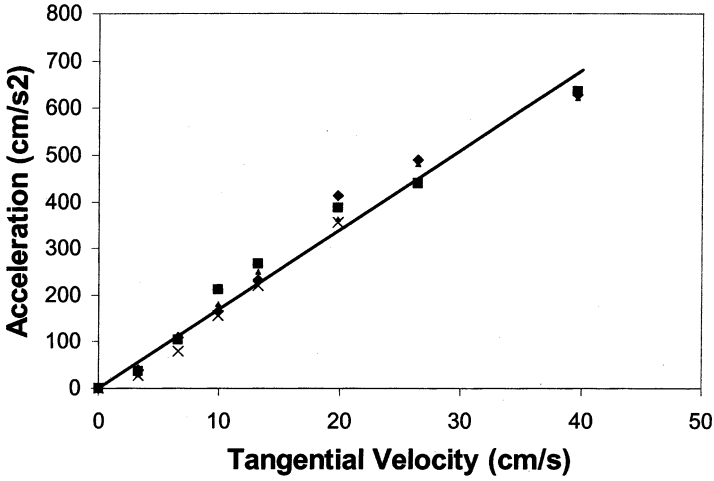

Figure 4 A plot of the maximum acceleration against the tangential velocity for all experiments; a near linear relationship is noted. Data is calculated from experiments in 6.3 cm (■), 9.5 cm (◇), 14.5 cm (▲), and 24.8 cm (×) diameter cylinders.

equation for l/r becomes

$$l/r = \beta\sqrt[3]{\Omega},\ \Omega \leq 30 \tag{5}$$

where $\beta = 0.37$ second$^{1/3}$. As l/r determines the shape of the velocity profile, experiments run at the same rotation rate should show qualitatively similar velocity profiles, regardless of cylinder size.

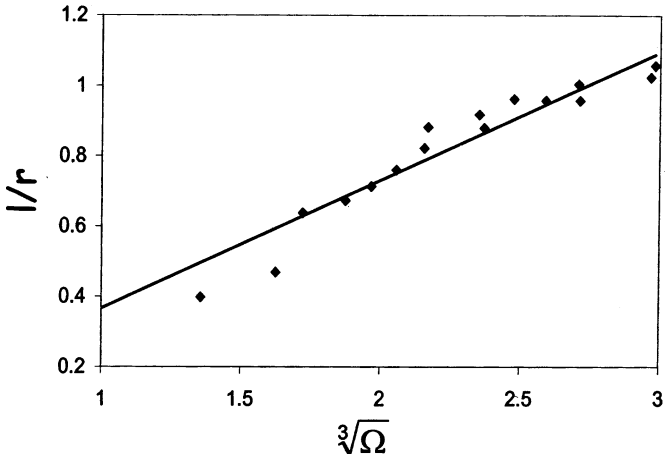

Figure 5 The value of l/r is plotted against the cube root of rotation rate, showing a linear relationship.

Developing a Model

The simplest possible model for particle velocity relates velocity and distance when acceleration is constant

$$V^2 = V_0^2 + 2ax \tag{6}$$

where V_0 is the initial downstream velocity, and x is the downstream co-ordinate. Acceleration has been shown, though, to vary along the length of the flowing region. Also, the distance to reach zero acceleration depends on the rotation rate. It may be possible, however, to scale peak velocities using Equation (6), subject to some simplifying assumptions:

1. particles emerge into the flowing layer with zero initial downstream velocity ($V_0 = 0$),
2. peak acceleration is proportional to the TV, Equation (4),
3. particles accelerate over the distance l,
4. acceleration (a) is not constant over the distance l, but the rate of change in acceleration scales appropriately with the value of l [i.e., $a = a_{\max} f(x/l)$, x is the distance down the cascade].

Using these assumptions and Equations (4–6), a new relation for particle velocity would be

$$V = R\Omega^{2/3}\sqrt{2\pi\alpha\beta} \tag{7}$$

Equation (7) relates particle velocities to the rotation rate and the radius and can be used as the basis for scaling particle velocities with changes in cylinder diameter and rotation rate.

Returning to Dimensional Analysis

Equation (7) gives a relationship between velocity, rotation rate, and cylinder radius that can be used to complete the dimensional analysis discussed earlier. Applying dimensional homogeneity and solving leads to

$$V = kR\Omega^{2/3}\left(\frac{g}{d}\right)^{1/6} \tag{8}$$

To test the scaling criteria suggested by Equation (8), we will look at velocity profiles between 10 and 30 rpm. Figure 6A shows the scaled velocity profiles [i.e., all data is divided by using $V = KR\Omega^{2/3}\,(g/d)^{1/6}$ and the distance down the cascade is divided by the cylinder diameter] for experiments run between 10 and 30 rpm (the unscaled data is shown in Figure 6B). We see very good agreement in velocity magnitudes across all rotation rates and cylinder sizes (which incorporate a 4× range in vessel radii and a 3× range in rotation rates).

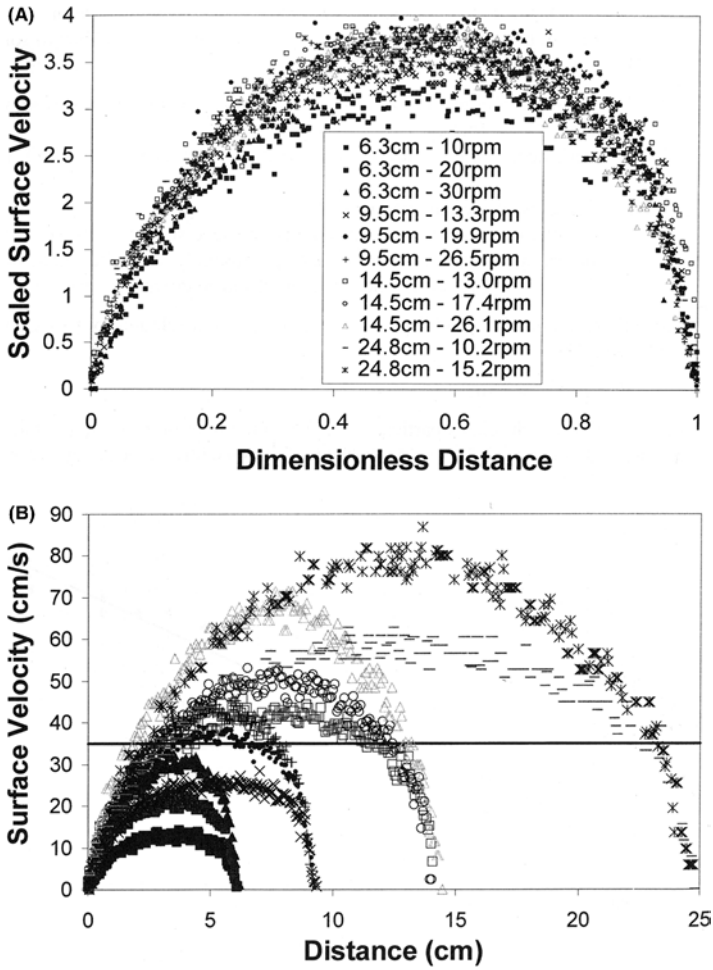

Figure 6 (**A**) Scaled velocity profiles for all experiments run between 10 and 30 rpm and in (**B**) the unscaled profiles.

Equation (8) indicates that particle size has an independent and measurable, although small, effect on particle velocities, which is further discussed elsewhere (19).

Returning to our example of scaling from 5 to 25 ft^3 blender, again the relative change in length is 71%. This time, in ordre to scale surface velocities using this approach, the blending speed (Ω) must be reduced by a factor of $(1.71)^{-3/2} = 0.45$, corresponding to 6.7 rpm (assuming the particle diameter, d, remains constant). Again, the total number of revolutions would remain constant at 225 for a blend time of 33.6 minutes.

TESTING VELOCITY SCALING CRITERIA

Experimental work has not validated the scaling procedure above with respect to scale-up of blending processes. Since this approach also relies on empirical work, this model should not be favored over other approaches currently in use, though it may provide additional insights.

However, recent work has indicated that particle velocities may be critical for determining segregation dynamics in double cone blenders and V-blenders (20,21). Segregation occurs within the blender as particles begin to flow in regular, defined patterns that differ according to their particle size. Experimental work demonstrates how this occurs. In a 1.9 qt. capacity V-blender at fixed filling (50%), incrementally changing rotation rate induced a transition between two segregation patterns, as seen in Figure 7A. At the lower rotation rate, the "small out" pattern forms; the essential feature of the "small out" pattern is that the smaller red particles dominate the outer regions of the blender while the larger yellow particles are concentrated near the center. At a slightly higher rotation rate, the "stripes" pattern forms, in this case, the small particles form a stripe near the middle of each shell in

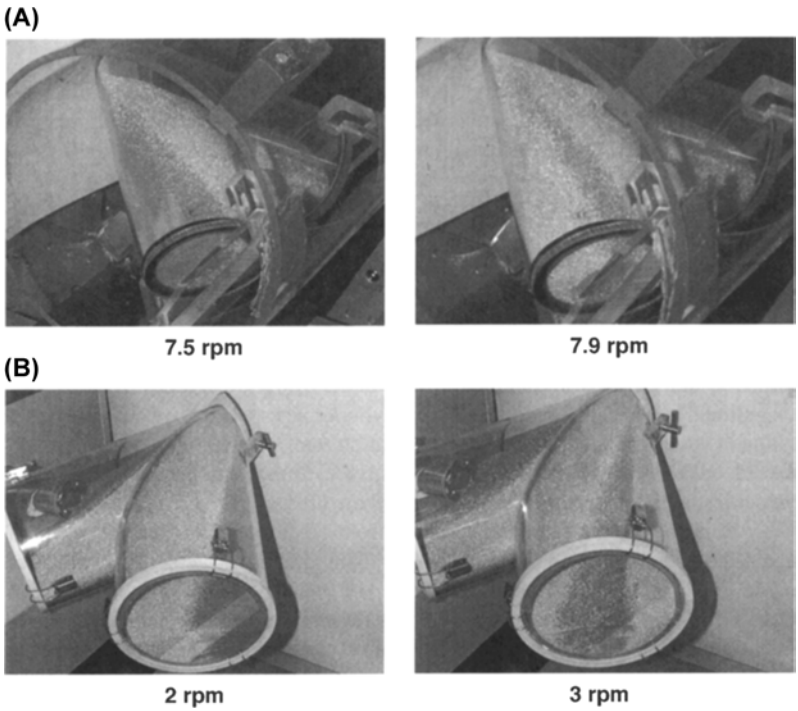

Figure 7 Changes in segregation pattern formation in the (**A**) 1.9 quart and (**B**) 12.9 quart V-blenders.

Table 2 Vessel Dimensions

Nominal capacity	Vessel volume (quarts)	L (cm)	R (cm)	D (cm)	θ
1P	0.8	10.5	7.9	6.7	80°
1Q	1.9	13.9	10.6	9.2	80°
4Q	6.5	21.2	14.6	13.8	75°
8Q	12.9	24.7	18.8	17.6	75°
16Q	26.5	33	24.2	21.6	75°

the blender. Both patterns are symmetrical with respect to the central vertical symmetry plane orthogonal to the axis of rotation.

To validate both the particle velocity hypothesis and our scaling criteria, similar experiments were run in a number of different capacity V-blenders. Vessel dimensions are shown in Table 2, along with a schematic, shown in Figure 8.

All the vessels are constructed from clear plexiglas, enabling visual identification of segregation patterns.

For these experiments, a binary mixture of sieved fractions of 150–250 μm (nominally 200 μm) and 710–840 μm (nominally 775 μm) glass beads was used. A symmetrical initial condition (top-to-bottom loading) is implemented. The blender is run at constant rotation rate; a segregation pattern was assumed to be stable when it did not discernibly change for 100 revolutions. In many pharmaceutical operations, the mixing time is on the order of 100–500 revolutions, and experiments are run with regard to this timeframe.

The transition speeds (rotation rates) were determined for the change from the "small out" pattern to "stripes" at 50% filling for all the blenders listed in Table 2 (Figure 7 shows results from the 1.9 and 12.9 qt. blenders). As discussed earlier, the most commonly accepted methods for scaling tumbling blenders have used one of two parameters, either the Fr or the tangential speed of the blender. Earlier, we derived $V = KR\Omega^{2/3}(g/d)^{1/6}$ and showed that it effectively scales particle velocities when the rotation rate is below 30 rpm. We note that all three of these criteria indicate an inverse relationship between

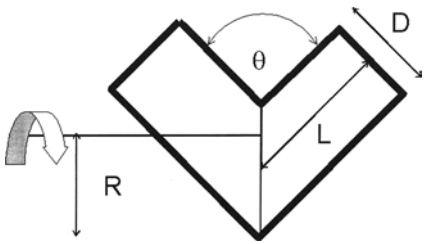

Figure 8 A sketch of the relevant dimensions for a V-blender; the actual values for the five blenders used are shown in Table 3.

Table 3 Parameter Values at Transition RPM

Blender size	Transition rotation rate	Fr, $\Omega^2 R/g$ ($\times 10^5$)	Tangential velocity, ΩR (cm/sec)	$R\Omega^{2/3}\,(g/d)^{1/6}$ (cm/sec)
1P	9.5	20	7.9	9.9
1Q	7.7	18	8.5	11.5
4Q	3.5	5	5.4	9.4
8Q	2.5	3	4.9	9.6
16Q	1.7	2	4.3	9.6

Abbreviations: RPM, revolutions per minute; *Fr*, Froude number.

rotation rate and blender size. Table 3 shows the parameter values at the transition rotation rate for $R\Omega^{2/3}(g/d)^{1/6}$, Fr, and the TV. $V = KR\Omega^{2/3}(g/d)^{1/6}$ parameter gives much better agreement than either Fr or TV; the relative standard deviation (RSD) for $V = KR\Omega^{2/3}(g/d)^{1/6}$ is 8.5%, compared to 89% for Fr and 30% for TV.

THE EFFECTS OF POWDER COHESION

A substantial problem that remains open is how to account for the effect of cohesion of powder flow and scale-up, in particular for mixing operations. The problem is extensive, and only a brief discussion is provided here.

In simple terms, a cohesive powder can be defined as a material where the adhesive forces between particles exceed the particle weight by at least an order of magnitude. In such systems, particles no longer flow independently; rather, they move in "chunks" whose characteristic size depends on the intensity of the cohesive stresses.

The effective magnitude of cohesive effects depends primarily on two factors: the intensity and nature of the cohesive forces (e.g., electrostatic, van der Waals, capillary) and the packing density of the material (which determines the number of interparticle contacts per unit area). This dependence on density is the source of great complexity: cohesive materials often display highly variable densities that depend strongly on the immediate processing history of the material.

In spite of this complexity, a few "guidelines" can be asserted within a fixed operational scale:

1. slightly cohesive powders mix faster than free flowing materials,
2. strongly cohesive powders mix much more slowly,
3. strongly cohesive powders often require externally applied shear (in the form of an impeller, and intensifier bar, or a chopper),
4. baffles attached to vessels do not increase shear substantially.

Lacking a systematic means to measure cohesive forces under practical conditions, the effects of cohesion on scale-up have been rarely studied. The most important observation is that cohesive effects are much stronger in smaller vessels, and their impact tends to disappear in larger vessels. The reason is simple: while cohesive forces are surface effects, the gravitational forces that drive flow in tumbling blenders are volume effects. Thus, as we increase the scale of the blender, gravitational forces grow faster, overwhelming cohesive forces. This can also be explained by remarking that the characteristic "chunk" size of a cohesive powder flow is a property of the material, and thus to a first approximation, it is independent of the blender size. As the blender grows larger, the ratio of the "chunk" size to the blender size becomes smaller.

Both arguments can be mathematically expressed in terms of a dimensionless "cohesion" number Π_c

$$\Pi_c = \sigma/\rho g R = s/R,$$

where σ is the effective (surface averaged) cohesive stress (under actual flow conditions), ρ the powder density under flow conditions, g the acceleration of gravity, and R is the vessel size. The group $s = \sigma/\rho g$ is the above- mentioned "chunk" size, which can be more rigorously defined as the internal length scale of the flow.

Thus, as R increases, Π_c decreases. This is illustrated in Figure 9, which shows the evolution of the RSD of a blending experiment in a small V-blender for three mixtures of different cohesion. Three systems were studied: a low cohesion system composed of 50% Fast-Flo Lactose and 50% Avicel 102; a medium cohesion system composed of 50% Regular Lactose and 50% Avicel 102, and a high cohesion system composed of 50% Regular Lactose and 50% Avicel 101. In all cases, an aliquot of the system was laced with 6% micronized acetaminophen, which was used as a tracer to determine the axial mixing rate in V-blenders of different capacities (1Q, 8Q, and 28Q).

Core sampling was used to gather 35–70 samples per experimental time point from three cores across each half of the blender. Samples were quantified using NIR spectroscopy, which was shown to be an accurate and efficient method for quantifying mixture quality. A simple model was used to determine mixing rates for both top/bottom and left/right loaded experiments. Variance measurements were split into axial and radial components to give more insight into mixing mechanisms and the separate effects of cohesion and vessel size on these mechanisms.

Convective mixing rates for radially segregated (top/bottom) loading were nearly constant regardless of changes in vessel size or mixture cohesion. Measured variances at short mixing times (i.e., five revolutions) were highly variable. These variations were attributed to unpredictable cohesive flow patterns during the first few rotations of the blender. An important conclusion was that scale-up of radial mixing processes could be obtained by simply allowing for a few (fewer than 10) "extra" revolutions to cancel this variability. As long

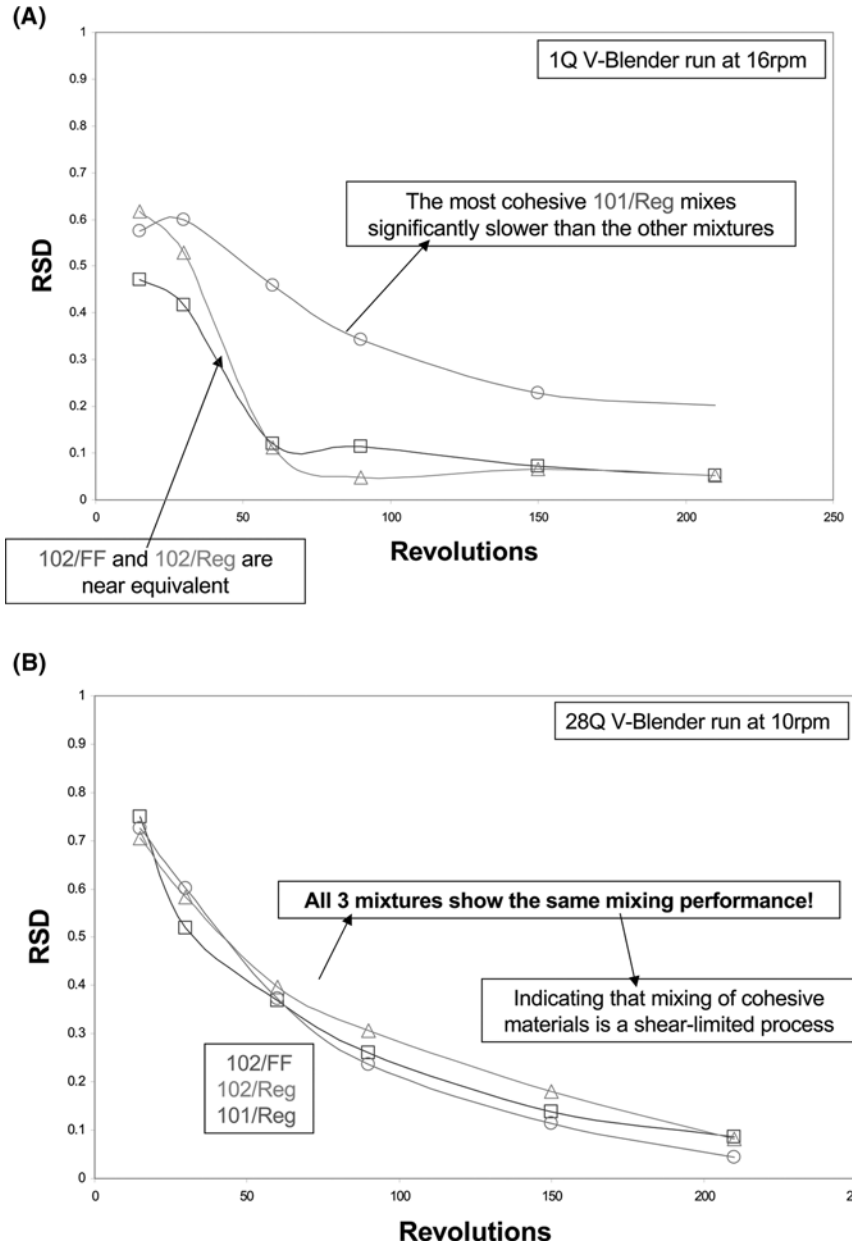

Figure 9 (**A**) Relative standard deviation measured for axially segregated blends of different cohesion in a 1-quart V-blender. As cohesion increases, blending becomes slower. (**B**) Relative standard deviation measured for axially segregated blends of different cohesion in a 28-quart V-blender. In a large vessel, the effects of cohesion become unimportant.

as the shear limit was reached, the mixing rates was the same for all mixtures and vessel sizes, indicating that required mixing times (in terms of revolutions) needed to insure process outcome could be kept constant regardless of mixture cohesion or mixer size.

However, for axially segregated (left/right) loading, the scale-up factors depended on cohesion, indicating that scale-up is a mixture-dependent problem. As shown in Figure 9A, the most cohesive system mixed much more slowly in the smaller (1Q) blender. However, all three systems mixed at nearly the same rate in the larger (28Q) vessel (Fig. 9B).

The conclusion from these results is that lab scale experiments for cohesive powders are of questionable validity for predicting full-scale behavior. Behavior at small scales is likely to be strongly affected by cohesive effects that are of much less intensity in the large scale. Moreover, the density of the powder, and therefore the intensity of cohesive effects, might also depend on vessel size and speed. An additional important comment is that the discussion presented in this section does not address another important cohesion effect: API agglomeration. As particles become smaller, cohesive effects grow larger. At some point, agglomeration tendencies become very significant.

The critical factor in achieving homogeneity becomes the shear rate, which is both scale- and speed-dependent.

In summary, scale-up and scale-down of blenders for cohesive powders is a risky enterprise. Caution is strongly advised.

RECOMMENDATIONS AND CONCLUSIONS

The analysis of particle velocities provides a good first step toward the rigorous development of scaling criteria for granular flow, but it is far from conclusive. For free flowing systems, while particle velocities may control the development of segregation patterns in small capacity V-blenders, velocity may not be the most important dynamical variable affecting the mixing rate. If we regard mixing and segregation as competing processes, however, then knowing that one is velocity dependent and the other is not could be significant. Earlier, we discussed that mixing rate shows little change with rotation rate but large variation with changes in fill level. These results may indicate that a proportionality factor such as (mass of contents in motion)/(total mass) may be important for scaling the mixing process. It is important in granular systems to first determine the dynamical variable that governs the process at hand before determining scaling rules—the basic caveats that particle size, particle velocities, flowing layer depth, or the relative amount of particles in motion may all play a role in a given process, making it important to identify the crucial variables *before* attempting scale-up.

A systematic, generalized approach for the scale-up of granular mixing devices is still far from attainable. Clearly, more research is required both to test current hypotheses and to generate new approaches to the problem.

Still, we can offer some simple guidelines that can help the practitioner wade through the scale-up process:

1. Make sure that changes in scale have not changed the dominant mixing mechanism in the blender (i.e., convective to dispersive). This can often happen by introducing asymmetry in the loading conditions.
2. For free flowing powders, number of revolutions is a key parameter but rotation rates are largely unimportant.
3. For cohesive powders, mixing depends on shear rate, and rotation rates are very important.
4. When performing scale-up tests, be sure to take enough samples to give an "accurate" description of the mixture state in the vessel. Furthermore, be wary of how you interpret your samples; know what the mixing index means and what your confidence levels are.
5. One simple way to increase mixing rate is to decrease the fill level—while this may be undesirable from a throughput point of view, decreased fill level also reduces the probability that dead zones will form.
6. Addition of asymmetry into the vessel, either by design or the addition of baffles, can have a tremendous impact on mixing rate.

Until rigorous scale-up rules are determined, these cautionary rules are the "state of the art" for now. We offer a first step toward rigorous scaling rules by scaling particle surface velocities but caution that this work is only preliminary in nature. The best advice is to be cautious—understand the physics behind the problem and that statistics of the data collected. Remember that a fundamental understanding of the issues is still limited and luck is unlikely to be on your side, hence frustrating trial-and-error is still likely (and unfortunately) necessary to be employed.

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7

Powder Handling

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INTRODUCTION

The goal in any blending operation is to have a properly blended powder mixture at the point in the process where it is needed, for example, during filling of the tablet die. This is not at all the same as requiring that all constituent powders in a blender be properly blended, since subsequent handling of a well-blended powder can result in significant deblending due to segregation. Segregation is as much a threat to product uniformity as poor or incomplete blending. An ability to control particle segregation during powder handling and transfer is critical to producing a uniform product. Understanding the flow behavior in bins and hoppers is a vital necessity for understanding segregation tendencies. Further consideration must be given to maintaining a reliable flow of powder, since no flow or erratic flow can slow production or stop a process altogether.

The balance of this chapter will focus on achieving the uniformity requirements for the product, given that a well-mixed blend has been achieved in the blender. Typical processing steps will be reviewed. The major concerns with powder flow through these steps will be illustrated, along with methods to determine the flow behavior in these processes. The mechanisms of segregation and methods to identify problems will be presented. Finally, after an understanding of these processes, scaling issues will be discussed.

Upon first reading the balance of this chapter, the reader will undoubtedly call into question why, in a chapter on blending, there is heavy emphasis

on flow behavior in bins or a discussion of flow properties. The author's experience is that many pharmaceutical companies are equally likely to have problems with producing a well-mixed blend and having an otherwise acceptable blend segregate upon further handling. Further, many firms have sufficient knowledge to diagnose and solve blending problems but lack understanding of the powder flow behavior that results in the content uniformity problem they may be facing. Lastly, these problems of no flow and segregation are less likely to occur at smaller scales and often appear for the first time at the full-scale batch, long after clinical trials are complete and the formulation and processing equipment are cast in stone.

REVIEW OF TYPICAL POWDER TRANSFER PROCESSES

Powder that has been blended in a blender must be discharged for further processing. Often, discharge is driven by gravity alone (such as out of a V-blender), though powder may also be forced out of the blender by way of mechanical agitation (e.g., a ribbon blender). The powder is often discharged into one or more portable containers, such as bins or drums, though some form of conveying system, such as vacuum transfer, may also be used. If drums are used, powder may be hand-scooped from the drums into downstream equipment, or a hopper may be placed on the drum, followed by inversion of the drum for gravity discharge. Powder in bins is usually discharged by gravity alone. Powder then feeds into one or more press hoppers, either directly or through a single or bifurcated chute, depending on the press configuration. With many modern presses, powder is fed by way of a feed frame or powder feeder from the press hopper into the die cavities.

Each of these transfer and handling steps is deceptively simple. Each of these steps can have a dramatic effect on the product quality, even if no effect is desired. Powder transfer should not be taken for granted and instead should be considered a critical unit operation for which bins, chutes, and press hoppers are major design-critical pieces of equipment.

CONCERNS WITH POWDER-BLEND HANDLING PROCESSES

There are two primary concerns with powder handling that cannot be overlooked when scaling processes: achieving reliable flow and maintaining blend uniformity. To address these issues when scaling processes, knowledge of how powders flow and segregate is required.

How Do Powders Flow?

A number of problems can develop as powder flows through equipment such as bins, chutes, and press hoppers. If the powder has cohesive strength,

an arch or rathole may form. An *arch* is a stable obstruction that usually forms within the hopper section (i.e., converging portion of the bin) near the bin outlet. Such an arch supports the rest of the bin's contents, preventing discharge of the remaining powder. A *rathole* is a stable pipe or vertical cavity that empties out above the bin outlet. Powder remains in stagnant zones until an external force is applied to dislodge it. *Erratic flow* is the result of the blend's alternating between arching and ratholing, while *flooding* or *uncontrolled flow* may occur if a rathole spontaneously collapses. On the other hand, a deaerated bed of fine powder may experience flow rate limitations or no-flow conditions.

One of the most important factors in determining whether powder will discharge reliably from bins or hoppers is establishing the flow pattern that will develop as powder is discharged. The flow pattern is also critical in understanding segregation behavior.

Flow Patterns

Two flow patterns can develop in a bin or hopper: funnel flow and mass flow. In funnel flow (Fig. 1), an active flow channel forms above the outlet, which is surrounded by stagnant material. This is a first-in, last-out flow sequence. As the level of powder decreases, stagnant powder may slough into the flow channel if the material is sufficiently free flowing. If the powder is cohesive, a stable rathole may remain.

In mass flow (Fig. 2), all of the powder is in motion whenever any is withdrawn. Powder flow occurs throughout the bin, including at the walls.

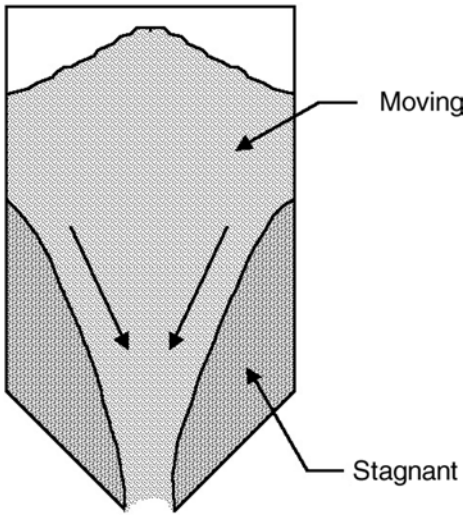

Figure 1 Funnel flow behavior in a bin.

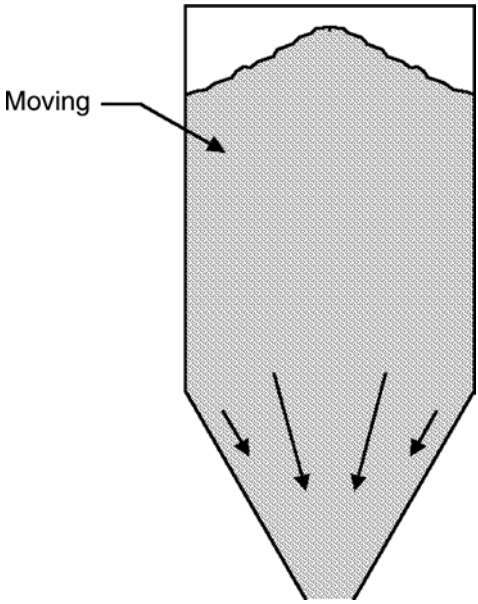

Figure 2 Mass flow behavior in a bin; all materials are moving during discharge.

Mass flow provides a first-in, first-out flow sequence, eliminates stagnant powder, provides a steady discharge with a consistent bulk density, and provides a flow that is uniform and well controlled.

Requirements for achieving mass flow include sizing the outlet large enough to prevent arch formation and ensuring the hopper walls are steep and smooth enough to allow flow along them. Several flow properties are relevant to making such predictions. These properties are based on a continuum theory of powder behavior—namely, that powder behavior can be described as a gross phenomenon without describing the interaction of individual particles. The application of this theory using these properties has been proven over the last 40 years in thousands of installations handling the full spectrum of powders used in industry (1).

Flow Properties

In order to select, design, retrofit, or scale-up powder handling equipment, knowledge of the range of flow properties for all of the powders to be handled is critical. Formulators can also use these properties during product development to predict flow behavior in existing equipment. Although there are many tests that measure "flowability," it is important to measure flow properties relevant to the flow of equipment in the actual process (2). The flow properties of interest to those involved with scale-up of processes include cohesive strength, wall friction, and compressibility.

Cohesive strength: The consolidation of powder may result in arching and ratholing within transfer equipment. These behaviors are related to the cohesive strength of the powder, which is a function of the applied consolidation pressure. Cohesive strength of a powder can be measured accurately by a direct shear method. The most universally accepted method is described in ASTM standard D 6128-00 (3).

By measuring the force required to shear a bed of powder that is under various vertical loads, a relationship describing the cohesive strength of the powder as a function of the consolidating pressure can be developed (4). This relationship, known as *a flow function*, FF, can be analyzed to determine the minimum outlet diameters for bins to prevent arching and ratholing.

Wall friction: Used in a continuum model, wall friction (friction of powder sliding along a surface) is expressed as the wall friction angle ϕ', or coefficient of sliding friction μ [where $\mu = \text{tangent}(\phi')$]. This flow property is a function of the powder handled and the wall surface in contact with it. The wall friction angle can be measured by sliding a sample of powder in a test cell across a stationary wall surface using a shear tester (Fig. 3) (4). Wall friction can be used to determine the hopper angles required to achieve mass flow. As the wall friction angle increases, steeper hopper walls are needed for powder to flow along them.

Bulk density: The bulk density of a given powder is not a single or even a dual value, but varies as a function of the consolidating pressure applied to it. The degree to which a powder compacts can be measured as a function of the applied pressure (4). For many materials, in a plot of the log of the bulk density, γ, versus log of the consolidating pressure, σ, a straightline curve fit is obtained. The resulting data can be used to accurately determine capacities for storage and transfer equipment of any scale, as well as to provide information to evaluate wall friction and feeder operation requirements.

If a flow problem is encountered in solids-handling equipment, at any scale, the most likely reason is that the equipment was not based on the flow properties of the material handled. Often, when flow problems are encountered, the group responsible for selecting handling equipment had little or no knowledge of flow patterns or flow properties.

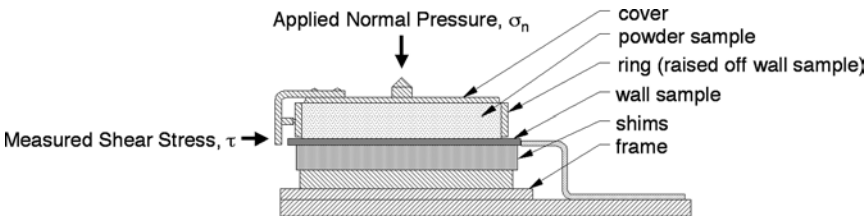

Figure 3 Setup of test apparatus for a wall friction test.

With an understanding of powder flow behavior and flow properties, segregation can be considered. Ultimately, as material is handled, stored, and transferred, the flow pattern that occurs will dictate how segregated the material will be when fed to downstream equipment.

How Do Powders Segregate?

Segregation is the unwanted separation of differing components of the blend. This separation action is often referred to as a segregation mechanism. A second action is required for segregation to manifest itself, specifically, the flow from the blender to the creation of the dose. As material flows, the segregated zones may be reclaimed in such a way as to be effectively reblended; or these zones may be reclaimed one at a time, exacerbating segregation.

Segregation Mechanisms

Segregation can take place whenever forces are applied to the powder, for example by way of gravity, vibration, or air flow. These forces act differently on particles with different physical characteristics, such as particle size, shape, and density. Most commonly, particles separate as a result of particle size differences. The result of segregation is that particles with different characteristics end up in different zones within the processing equipment (e.g., bin).

Typical pharmaceutical blends separate from each other by three common mechanisms: sifting/percolation, air entrapment (fluidization), and particle entrapment (dusting).

Sifting/percolation: Under appropriate conditions, fine particles tend to sift or percolate through coarse particles. For segregation to occur by this mechanism, there must be a range of particle sizes (a ratio of 2:1 is often more than sufficient). In addition, the mean particle size of the mixture must be sufficiently large (greater than about 100 μm), the mixture must be relatively free flowing, and there must be relative motion between particles. This last requirement is very important, since without it even blends of ingredients that meet the first three criteria will not segregate.

Relative motion can be induced, for example, as a pile is being formed, as particles tumble and slide down a chute. The result of sifting/percolation segregation is usually a side-to-side variation of particles. In the case of a bin, the smaller particles will generally be concentrated under the fill point, with the coarse particles concentrated at the outside of the pile (Fig. 4).

Air entrainment (fluidization): Handling of fine, aerated powders with variations in particle size or particle density often results in a vertical striation pattern, with the finer/lighter particles concentrated above larger/denser ones. This can occur, for example, during the filling of a bin. Whether

Figure 4 Photo of sifting segregation after pile formation; light-colored fines remain in the center, while darker, coarse particles concentrate at the perimeter.

or not the powder is pneumatically conveyed into the container or simply free-falls through an air stream, it may remain fluidized for an extended period after filling. In this fluidized state, larger and/or denser particles tend to settle to the bottom (Fig. 5). Air counterflow that occurs while filling an enclosed container can also cause these problems.

Particle entrainment (dusting): Similar to the air entrainment mechanism, particle entrainment, or dusting segregation, occurs primarily with fine powders that vary in particle size or density. Because of these variations, the finer/lighter particles remain suspended in air longer than larger/denser ones. For example, when powder drops into a container, the larger/denser particles will tend to remain concentrated in an area near the incoming stream, whereas smaller/lighter particles will be transported into slower-moving or even stagnant air (Fig. 6). This problem is particularly acute with pyramidal bins, as airborne fines that settle toward the walls eventually slide to the valleys (corners) of the bins. The powder in the corners of the bin discharges last because of the funnel flow pattern that usually develops. The resulting trend across one bin usually involves a steady climb in the concentration of the finer components toward the end of the run.

Identifying Segregation Problems

At the bench-scale: Two basic bench-scale evaluations serve as relative indicators of potential segregation problems. Neither approach provides a quantitative result that correlates to what could be expected at a pilot or production scale; however, they can be used as an indicator of the potential problems that may lie ahead. One approach is to sieve that blend and then assay individual screen cuts. If there is a wide variation of the assay across

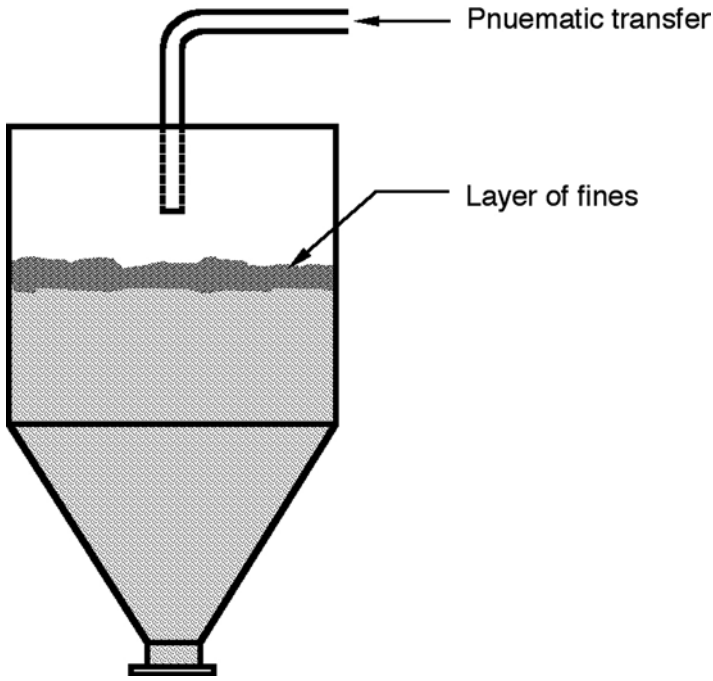

Figure 5 Fluidization segregation can take place when a bed of aerated material settles, driving fines to the top of the bin.

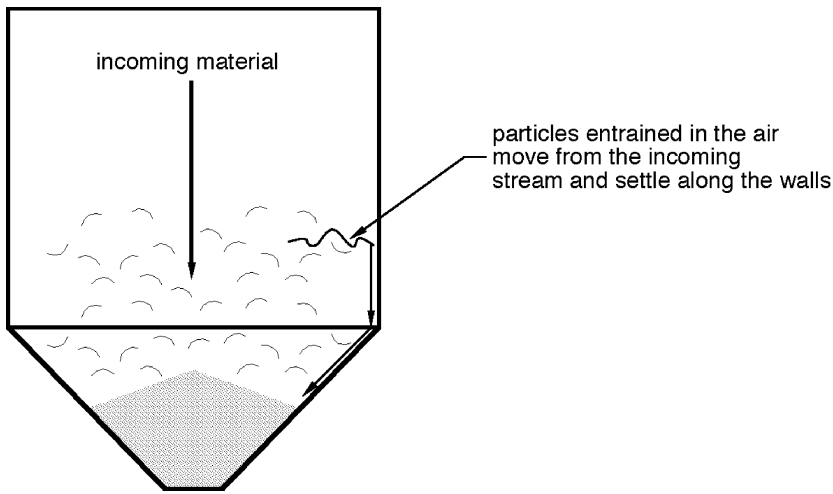

Figure 6 Dusting segregation can take place when airborne dust settles along the walls of a bin.

particle sizes, this serves as a warning that content uniformity problems may occur. The concern with this approach is that the sieving process may separate particles in a more vigorous manner than would be experienced in the actual process.

A second type of bench-scale evaluation is generically called a segregation test. In this type of test, the blend is subjected to forces expected to be induced in a "real" application. If the material is prone to segregation, these forces would segregate the material into different zones of the test apparatus. Samples are then collected and analyzed. Assay or particle size differences across different zones of the tester serve as a warning that segregation problems may occur. The quality of the information gleaned from these segregation tests is highly dependent upon the test method (how well the tester reproduces the forces induced in the process), as well as on avoiding sampling error (how samples from the segregation tester are collected, handled, and analyzed). Two examples of segregation test methods are given in ASTM standards D6940-03 and D6941-03 (7,8).

At a pilot or production scale: The effects of segregation are usually recognized by comparing the standard deviation of samples of the final product (dosage form) to those collected either within a blender or upon blender discharge. The best way to diagnose problems is to take stratified, nested samples of powder from within the blender of dosage forms through the production run (5). Segregation usually results in distinct trends across the run. To diagnose the problem, these trends must be correlated with the flow sequence (from the blender to the dosage formation) and the likely segregation mechanisms.

SCALE EFFECTS

At the smaller scale, powder may be discharged from the blender into one or more containers and then hand-scooped from these containers into a small press hopper. Seldom is a batch left in storage for a significant time after blending prior to compression. At this scale, the forces induced on the particles during bulk transport and handling are lower than full scale; further, distances across which the particles can separate are smaller, thereby reducing the tendency for segregation to occur. Hand-scooping obviates concerns about reliable discharge of powder from a bin. So if this process works well at the small scale, what must be considered when larger batch sizes are needed?

Analysis of Flow

In situations where a complete description of the physical behavior of a system is unknown, scale-up approaches often involve the use of dimensionless groups, as described in Chapter 1. Unlike flow behavior in a blender, the flow behavior of powder through bins and hoppers can be predicted by a complete mathematical relationship. In light of this, analysis of powder flow in a bin or

hopper by dimensional relationships would be superfluous and, as will be illustrated, irrelevant, since nondimensional groups cannot be derived.

Bin or Hopper Outlet Size

If gravity discharge is used, the minimum outlet size required to prevent arching is dependent upon the flow pattern that occurs. Regardless of the flow pattern, though, the outlet size is determined with the powder's flow function, which is measured by way of the cohesive strength tests described earlier.

The outlet size required to overcome no-flow conditions depends highly on the flow pattern that develops. If mass flow develops, the minimum outlet diameter, Bc, to overcome arching is (4):

$$Bc = H(\theta')f_{\text{crit}}/\gamma \tag{1}$$

$H(\theta')$ is a dimensionless function derived from first principles and is given by Figure 7 [for the complete derivation of $H(\theta')$, which is beyond the scope of this chapter, see Ref. 4]. f_{crit}, with units of force/area, is the unconfined yield strength at the intersection of the hopper flow factor (ff, a derived

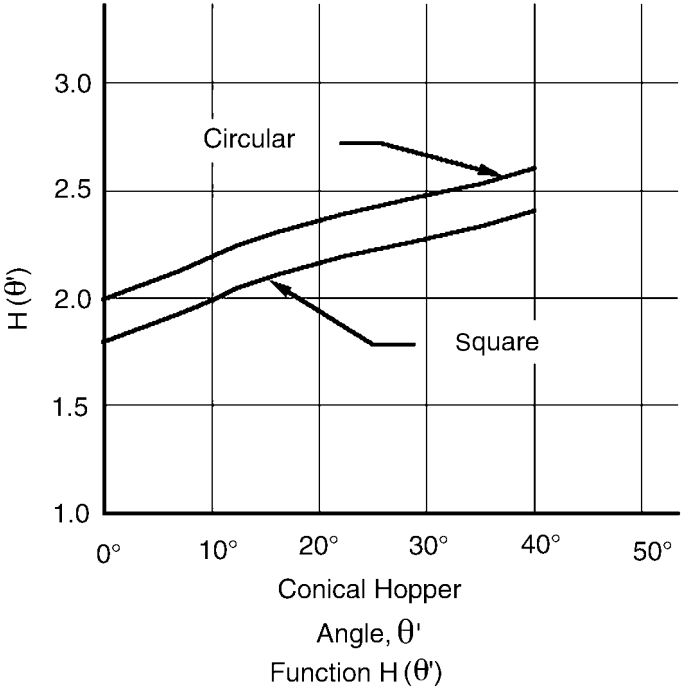

Figure 7 Plot showing derived function $H(\theta')$ used in calculating arching potential in mass flow bins.

function based on powder flow properties and the hopper angle) and the powder flow function (FF) (Fig. 8). Bulk density γ, with units of weight/volume, is the bulk density determined by compressibility tests described earlier. This calculation yields a dimensional value of *Bc* in units of length, which is scale independent. The opening size required is not a function of the diameter or the height of the bin or the height-to-diameter ratio.

In other words, as a formulation is developed, one can run the shear tests described earlier to determine the cohesive strength (flow function). This material-dependent flow function, in conjunction with Equation (1), will yield a minimum opening (outlet) size in order to avoid arching in a mass flow bin. For example, this opening size may be calculated to be 8 inches. This 8-inch diameter will be needed whether the bin holds 10 kilos or 1000 kilos, regardless of the hopper or cylinder height or diameter, and is scale independent. In this example, since an 8-inch-diameter opening is required, feeding this material through a press hopper or similarly small openings would pose real problems; it would be advisable to consider reformulating the product to improve flowability.

If funnel flow develops instead of mass flow, the minimum outlet diameter is given by the tendency for a stable rathole to occur, because this diameter is usually larger than that required to overcome arching. In this case, the minimum outlet diameter is

$$\mathrm{Df} = G(\phi t)fc(\sigma_1)/\gamma \tag{2}$$

$G(\phi t)$ is also a derived function and is given in Figure 9. $fc(\sigma_1)$, the unconfined yield strength of the material, is determined by the flow function (FF) at the actual consolidating pressure, σ_1. The consolidation pressure σ_1 is a function of the head or height of powder above the outlet of the bin, as given by Janssen's equation:

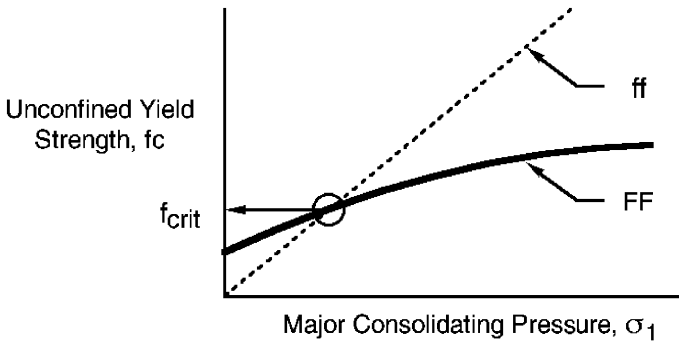

Figure 8 Sample flow function (FF) and flow factor (ff), showing f_{crit} at their intersection.

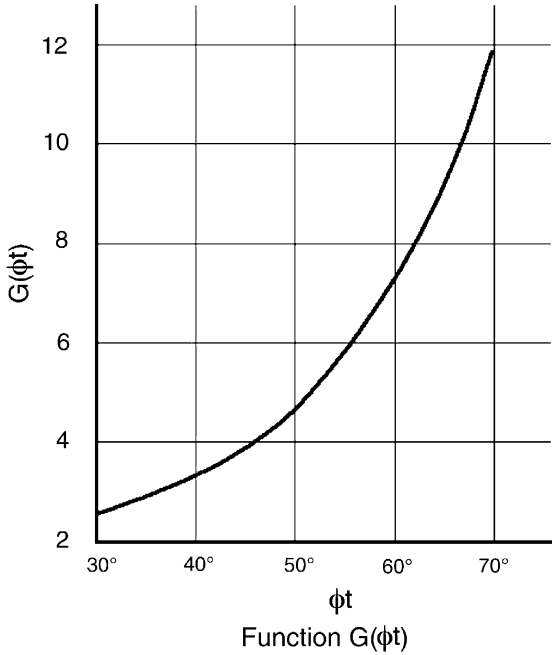

Figure 9 Plot showing derived function $G(\phi t)$ used in calculating ratholing potential in funnel flow bins.

$$\sigma_1 = (\gamma R/\mu k)(1 - e^{-\mu k h/R}) \tag{3}$$

where R is the hydraulic radius (area/perimeter), μ is the coefficient of friction (tangent ϕ'), k is the ratio of horizontal to vertical pressures (often, 0.4 is used), and h is the depth of the bed of powder within the bin.

This relationship in Equation (2) cannot be reduced further, for the function $fc(\sigma_1)$ is highly material-dependent.

Hopper Angle

Design charts describe which flow pattern would be expected to occur, dependent on the hopper angle (θc, as measured from vertical), wall friction angle (ϕ') and internal friction (δ) of the material being handled. An example of such a design chart for a conical hopper is shown in Figure 10. For any combination of ϕ' and θc that lies in the mass flow region, mass flow is expected to occur; if the combination lies in the funnel flow region, funnel flow is expected. The uncertain region is an area where mass flow is expected to occur but represents a 4° margin of safety on the design to account for inevitable variations in test results and surface finish.

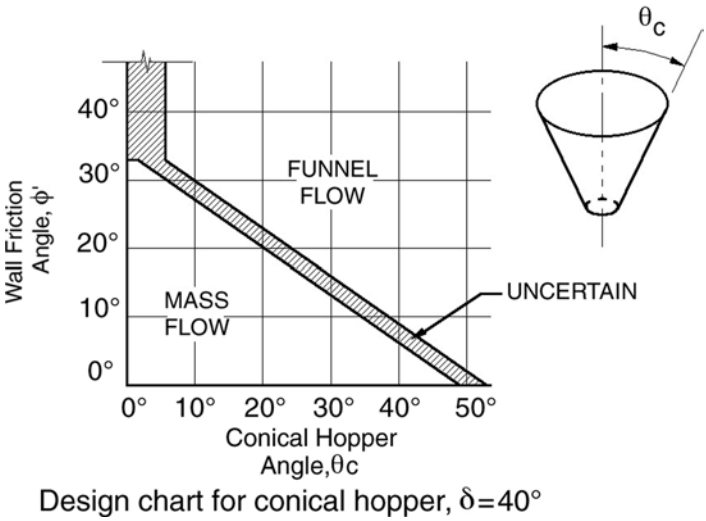

Figure 10 Mass flow/funnel flow design chart for a conical hopper handling a bulk material with a 40° effective angle of internal friction.

The wall friction angle ϕ' is determined by wall friction tests, as described earlier. The resulting wall yield locus (Fig. 11) is a function of the normal pressure against the surface. For many combinations of wall surfaces and powders, the wall friction angle changes depending on the normal pressure. When mass flow develops, the solids pressure normal to the wall surface is given by the following relationship:

$$\sigma_n = (\sigma'/\gamma b) \times \gamma B. \tag{4}$$

Equation 4 provides charts giving $(\sigma'/\gamma b)$. Assuming $(\sigma'/\gamma b)$ and the bulk density γ are constant for a given powder and hopper (a reasonable assumption for a first approximation), the pressure normal to the wall is simply a linear function of the span of the hopper, B, at any given point. Generally, ϕ' increases with decreasing normal pressure, σ_n. Therefore, the critical point is at the outlet of the hopper; this is the smallest span B, with the correspondingly lowest normal pressure to the wall, σ_n. Hence, this point usually has the highest value of wall friction for a given design, so long as the hopper interior surface finish and angle remain constant above the outlet.

When considering scale effects, the implication of the foregoing analysis is that the hopper angle required for mass flow is principally dependent on the outlet size selected for the hopper under consideration. Note that the

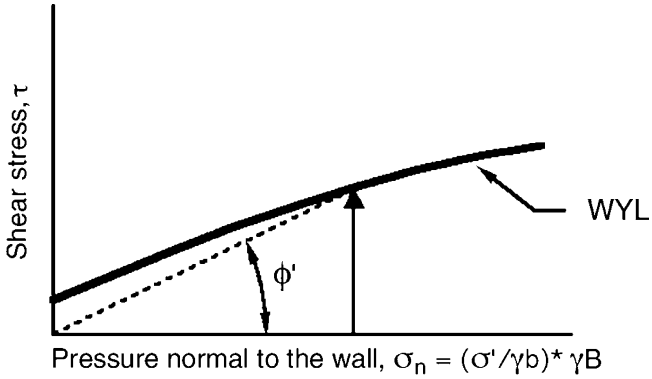

Figure 11 Sample wall yield locus generated from wall friction test data.

hopper angle required for mass flow is not a function of the flow rate, the level of powder within the hopper, or the diameter or height of the bin (as was also the case for minimum outlet size).

Since the wall friction angle generally increases with lower normal pressures, a steeper hopper is often required to achieve mass flow at smaller scales (smaller outlets). For example, assume that a specific powder discharges in mass flow from a bin with a certain outlet size. A second bin with an equal or larger outlet size will also discharge in a mass flow pattern for this powder, provided that the second bin has an identical hopper angle and surface finish. This is true regardless of the actual size of either bin; only the outlet size needs to be considered. The reverse, i.e., using the same hopper angle with a bin with a smaller outlet, will not always provide mass flow.

Of course, mass flow is highly dependent upon conditions below the hopper; a throttled valve, a lip or other protrusion, or anything that can initiate a zone of stagnant powder can convert any hopper into funnel flow, regardless of the hopper angle or surface finish.

In scaling the flow behavior of powders, it is better to rely on first principles and material flow properties, as opposed to reliance on observations or data gleaned from the initial scale.

Scaling Segregation

Although basic concepts are understood, equations based on the physics of segregation within bins are not well described. At best, a list of relevant variables can be described, but such a list would likely be incomplete. Even the process of mathematically describing a segregated powder bed beyond a "mixing index" is not well defined. After all, in addition to quantifying the variability, the spatial arrangement of the different zones is also significant. These limitations make even simple dimensional analyses of segregation

within bins impossible at this time. Instead, for the pharmaceutical scientist seeking guidance during scaling, there is heavy reliance on empirical considerations, experience, and judgment and on conservative design approaches. This may also put the scientist into a "hope-and-see" or reactionary position, an uncomfortable position, given the repercussions of product uniformity failure.

Avoiding Segregation

There are three basic approaches to defeat segregation (6):

1. Modify the powder in a way to reduce its inherent tendency to segregate.
2. Modify the equipment to reduce forces that act to segregate the powder.
3. Remedy segregation that takes place by reblending the powder dining subsequent transfer.

Modify the Powder to Reduce Its Tendency to Segregate

There are several ways to change the powder to reduce its tendency to segregate. One way is to change the particle size distribution of one or more of the components. If the components have a similar particle size distribution, they will generally have a lesser tendency to segregate. Another option is to change the particle size, such that the active segregation mechanism(s) become less dominant. For instance, one way to reduce fluidization segregation is to make the particles sufficiently large that the powder cannot fluidize. However, one must be careful in this approach not to activate a new segregation mechanism.

Another option is to change the cohesiveness of the powder, such that the particles in a bed of powder are less likely to move independently of each other. Increasing the tendency of one component to adhere to another will also reduce segregation. This is referred to as an ordered, adhesive, or structured blend. Granulation, whether wet or dry, is also implemented to, among other reasons, reduce segregation tendencies and improve powder flow. Bear in mind that, even if each particle is chemically homogeneous (which is never absolutely the case, even with granulations), segregation by particle size can result in variations that affect the end product, such as tablet weight or hardness.

Change the Equipment to Reduce the Chance of Segregation

Forces exerted on particles can induce segregation by many mechanisms. When handling a material where segregation is a concern, the designer must

minimize these forces. Unfortunately, there are no scaling criteria available for guidance. Worse yet, when scaling up, forces acting on the particles increase significantly, as well as distances across which the particles can separate.

Here are some general guidelines:

- *Minimize transfer steps.* With each transfer step and movement of the bin or drum, the tendency for segregation increases. Ideally, the material would discharge directly from the blender into the tablet press feed frame with no additional handling. In-bin blending is as close to this as most firms can practically obtain and is the best one can ask for—so long as a well-mixed blend can be obtained within the bin in the first place.
- *Minimize drop height.* Drop height serves to aerate the material, induce dust, and increase momentum of the material as it hits the pile, increasing the tendency for each of the three segregation mechanisms described earlier.
- *Control dust generation.* Dust can be controlled by way of socks or sleeves to contain the material as it drops from the blender to the bin, for example. Some devices are commercially available specifically for this purpose.
- *Control fluidization of powder.* Beware of processes, such as pneumatic conveying, that increase the potential for the material to become aerated.
- *Restriction.* Slowing the fill rate can reduce fluidization and dusting segregation tendencies.
- *Venting.* Air that is in an otherwise "empty" bin, for example, must be displaced from the bin as powder fills it. If this air is forced through material in the V-blender, perhaps sealed tight in the interest of containment, this can induce fluidization segregation within the blender. To avoid this, a separate pathway or vent line to allow the air to escape without moving through the bed of material can reduce segregation.
- *Distributor.* A deflector or distributor can spread the material stream as it enters the bin. Instead of forming a single pile, the material is spread evenly across the bin. This reduces sifting segregation but may cause additional dust generation, making dusting segregation worse.
- *Proper hopper, Y-branch design.* Press hoppers, transfer chutes, and Y-branches must be designed correctly to avoid stagnant material and to minimize air counterflow.
- *Operate the valve correctly.* Butterfly valves should be operated in full open position, not throttled to restrict flow. Restricting flow will virtually ensure a funnel flow pattern, which is usually detrimental to uniformity.

Change the Equipment to Provide Remixing

The concept of knowingly letting materials segregate and then counting on material transfer to provide reblending is frankly quite scary to pharmaceutical scientists, as well as to regulatory personnel. Make no mistake, however—this is a better approach than letting materials segregate and doing nothing about it. Ignorance is not bliss. The following concepts are not radical and, in fact, have been used for many decades in the pharmaceutical and other industries.

Use mass flow. In a mass flow pattern, material that has segregated in a side-to-side segregation pattern because of sifting or air entrainment will be reblended during discharge. In most applications, this reblending is sufficient to return the blend to its initial state of uniformity. However, a mass flow pattern will not remedy a top-to-bottom segregation pattern, such as that caused by fluidization segregation; the top layer will discharge last. Note that if top-to-bottom segregation occurs, funnel flow will simply result in the top layer discharging at some point in the middle of the run, and also will not provide any reblending.

Beware of velocity gradients. With mass flow, all the material is in motion during discharge, but the velocity will vary. The material will always be somewhat slower at the walls than at the center of the bin (assuming a symmetrical bin with a single outlet in the center). In critical applications, the velocity profile could affect uniformity, with the material at the walls discharging at a slightly slower rate than that from the center. While far superior to a funnel flow pattern, a mass flow pattern with high velocity gradients may not be desired. To remedy this, either a hopper that is designed well into the mass flow regime is needed, or a flow-controlling insert, such as a Binsert®, must be used. Velocity profiles, and their effect on blending material, can be calculated a priori, given the geometry of the bin and measured flow properties. As a point of interest, velocity profiles can be carefully controlled to force a bin to behave as a static blenders, as used in other industrial applications.

The scientist seeking to scale blending processes must be well aware of the limitations of the state of science in this area. Equal consideration must be given to the state of the blend in the blender, as well as the effects of subsequent handling.

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8

Scale-Up in the Field of Granulation and Drying

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INTRODUCTION

Today, the production of pharmaceutical granules is still based on the batch concept. In the early stage of the development of a solid-dosage form, the batch size is small, e.g., for first clinical trials. In a later stage, the size of the batch produced in the pharmaceutical production department may be up to 100 times larger. Thus, the scale-up process is an extremely important one. Unfortunately, in many cases, the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process, the quality of the granules may change. A change in the granule size distribution, final moisture content, friability, compressibility, and compactibility of the granules may strongly influence the properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, aging of the tablet, etc. In the following sections of this chapter, the scale-up process is analyzed, taking into account mathematical considerations of the scale-up theory (1), the search for scale-up invariants (2–5), and the establishment of in-process control methods (6–9), as well as the design of a robust-dosage form (10–13). In this respect, new

concepts, such as the percolation theory (13), play an important role. A new concept concerning a quasi-continuous production line of granules is presented (14–18). This concept permits the production of small-scale batches for clinical trials and of production batches using the same equipment. Thus, scale-up problems can be avoided in an elegant and cost-efficient way. Finally, the scale-up of the conventional fluidized bed spray granulation process is discussed, due to its common use for spray granulation and/or drying as a step subsequent to some type of wet granulation. The combination of reproducibility and batch size flexibility results in a highly efficient manufacturing method.

THEORETICAL CONSIDERATIONS

The Principle of Similarity

The Definition of Similarity and Dimensionless Groups

The important concept for scale-up is the principle of similarity (1–6). When scaling up any mixer/granulator (e.g., planetary mixer, high-speed mixer, pelletizing dish, etc.), the following three types of similarity need to be considered: geometric, kinematic, and dynamic. Two systems are geometrically similar when the ratio of the linear dimensions of the small-scale and scaled-up system are constant.

Two systems of different size are kinematically similar when, in addition to the systems being geometrically similar, the ratio of velocities between corresponding points in the two systems are equal. Two systems of different size are dynamically similar when *in addition* to the systems being geometrically and kinematically similar, the ratio of forces between corresponding points in the two systems are equal.

Similarity criteria: There are two general methods of arriving at similarity criteria:

1. when the differential equations or, in general, the equations that govern the behavior of the system, are known, they can be transformed into dimensionless forms,
2. when differential equations or, in general, equations that govern the behavior of a system, are not known, such similarity criteria can be derived by means of dimensional analysis.

Both methods yield dimensionless groups, which correspond to dimensionless numbers (1), e.g., Re, Reynolds number; Fr, Froude number; Nu, Nusselt number; Sh, Sherwood number; Sc, Schmidt number; etc. (2). The classical principle of similarity can then be expressed by an equation of the form:

$$\pi_1 = F(\pi_2, \pi_3, \ldots) \tag{1}$$

This equation may be a mechanistic (case A) or an empirical one (case B):

Case A

$\pi_1 = e^{-\pi_2}$ with the dimensionless groups:

$$\pi_1 = \frac{p(x)}{p(0)}$$

$P(x)$ = pressure at level x, $P(0)$ = pressure above sea level ($x = 0$)

$$\pi_2 = \frac{E(x)}{RT} \tag{2}$$

with $E(x) = Mgx$,

where $E(x)$ is the molar potential energy, M is the molecular weight, g is the gravitational acceleration, x is the height above sea level, and RT is the molar kinetic energy.

Case B

$$\pi_1 = a(\pi_2)^b(\pi_3)^c \tag{3}$$

The unknown parameters a, b, and c are usually determined by nonlinear regression calculus.

Buckingham's Theorem

For a correct dimensional analysis, it is necessary to consider Buckingham's theorem, which may be stated as follows (3,4):

1. The solution to every dimensionally homogeneous physical equation has the form $F(\pi_1, \pi_2, \pi_3, \ldots), = 0$, in which π_1, π_2, π_3,ô ... represent a complete set of dimensionless groups of the variables and the dimensional constants of the equation.
2. If an equation contains n separate variables and dimensional constants, and these are given dimensional formulas in terms of m primary quantities (dimensions), the number of dimensionless groups in a complete set is $(n-m)$.

THE DRY-BLENDING OPERATION

The dry-blending operation is a critical process in case of low-dosage forms. In order to obtain a high degree of mixing, cohesive powder components have to be disagglomerated. For this purpose, it is often advantageous to proceed as follows:

1. dry blending of the powder components,
2. sieving of the blend through a sieve with an appropriate mesh for disagglomeration,
3. final dry-blending step.

The shear forces at work during the sieving step are important for disagglomeration of the finer cohesive material and/or favoring contacts between finer and coarser particles.

In the case of an active substance at very low dose, i.e., requiring a high dilution with the auxiliary substances (e.g., 1:100), the blending operation may be divided into two steps: primary 1:10 dilution and then a second 1:10 blending step in order to obtain the final dilution.

The content uniformity which can be obtained depends, according to established theoretical considerations, on the particle size of the active substance (19,20). As a rough estimate for the obtainable relative standard deviation S_{rel} of the content of the active substance, the following rule can be applied, based on Poisson statistics:

$$S_{rel}(\%) = \frac{1}{\sqrt{N}} \times 100\%, \tag{4}$$

where N = number of particles of the active substance in a unit dose such as a tablet.

Thus, for a relative standard deviation of 1%, at least 10,000 particles of the active substance have to be distributed randomly in the tablet.

Let us illustrate with the following two examples to get an estimate of the particle size of a drug: tablet with a total mass of 100 mg shall contain 1 mg of drug substance. The drug substance has a true density of 1 g/cm^3. In this first example, we assume that we have 1 mg distributed as $N = 49$ fine particles having an ideal cubic form with a side length d, i.e., the volume of one particle is equal to d^3. Thus, as a particle size d we get 273 μm. According to Equation (4), the relative standard deviation $s_{rel} = \pm 14.3\%$. This first example leads to a relative standard deviation and content uniformity of a drug which is not acceptable. Thus, in a second example, the number of particles needs to be increased to at least $N = 10{,}000$.

In case of $N = 10{,}000$, the particle size of a drug substance becomes $d = 4.6$ μm. Thus, the drug needs to be micronized as a first step before the mixing operation. In case of the scale-up exercise of a low-dosage form, it is essential to check carefully that the active substance consisting of fine particles cannot form agglomerates but has been successfully disagglomerated. Thus, in an optimal case, the fine drug particles become "fixed" on the surface of the coarse particles of an appropriate diluent. In many cases, a subsequent wet agglomeration step in a high shear mixer can further improve the degree of mixing.

SCALE-UP AND MONITORING OF THE WET GRANULATION PROCESS

Dimensionless Groups

As the behavior of the wet granulation process cannot be described so far adequately by mathematical equations, the dimensionless groups have to

be determined by a dimensional analysis. For this reason, the following idealized behavior of the granulation process in the high-speed mixer is assumed:

- the particles are fluidized,
- the interacting particles have similar physical properties,
- there is only a short-range particle–particle interaction,
- there is no system property equivalent to viscosity, i.e.,

(1) there are no long-range particle–particle interactions and
(2) the viscosity of the dispersion medium air is negligible.

According to Buckingham's theorem, the following dimensionless groups can be identified:

$\pi_1 = \frac{P}{r^5\omega^3\rho}$ power number,

$\pi_2 = \frac{qt}{V\rho}$ specific amount of granulation liquid,

$\pi_3 = \frac{V}{V^*}$ fraction of volume loaded with particles,

$\pi_4 = \frac{r\omega^2}{g}$ Froude number (centrifugal/gravitational energy),

$\pi_5 = \frac{r}{d}$ geometric number (ratio of characteristic lengths).

List of symbols:

P	power consumption,
r	radius of the rotating blade (first characteristic length of the mixer),
ω	angular velocity,
ρ	specific density of the particles,
q	mass (kg) of granulating liquid added per unit time,
t	process time,
V	volume loaded with particles,
V^*	total volume of the vessel (mixer unit),
g	gravitational acceleration,
d	diameter of the vessel (second characteristic length of the mixer).

In principle, the following scale-up equation can be established:

$$\pi_1 = a(\pi_2)^b(\pi_3)^c(\pi_4)^d(\pi_5)^e \tag{5}$$

In general, however, it may not be the primary goal to know exactly the empirical parameters a, b, c, d, and e of the process under investigation, but to check or monitor pragmatically the behavior of the dimensionless groups (process variables and dimensionless constant) in the small- and

large-scale equipment. The ultimate goal would be to identify scale-up invariants.

Experimental Evidence for Scale-Up Invariables

In the case of the wet granulation process in a mixer/kneader, the granulation process can be easily monitored by the determination of the power consumption (6–9) (Fig. 1).

The typical power profile consists of five different phases (Fig. 2). Usable granulates can be produced in a conventional way only within the plateau region S_3–S_4 according to the nomenclature in Figure 2. As Figure 3 indicates, changing the type of mixer has only a slight effect on the phases of the kneading process.

However, the actual power consumption of mixers of different type differs greatly for a given granulate composition.

The important point is that the power consumption profile, as defined by the parameters S_3, S_4, and S_5, is independent of the batch size. For this investigation, mixers of the planetary type (Dominici, Glen, and Molteni) were used.

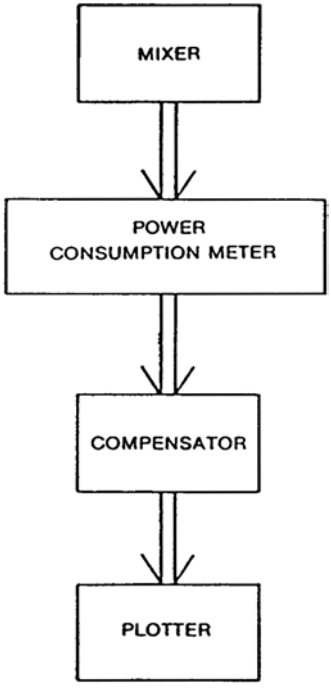

Figure 1 Block diagram of measuring equipment.

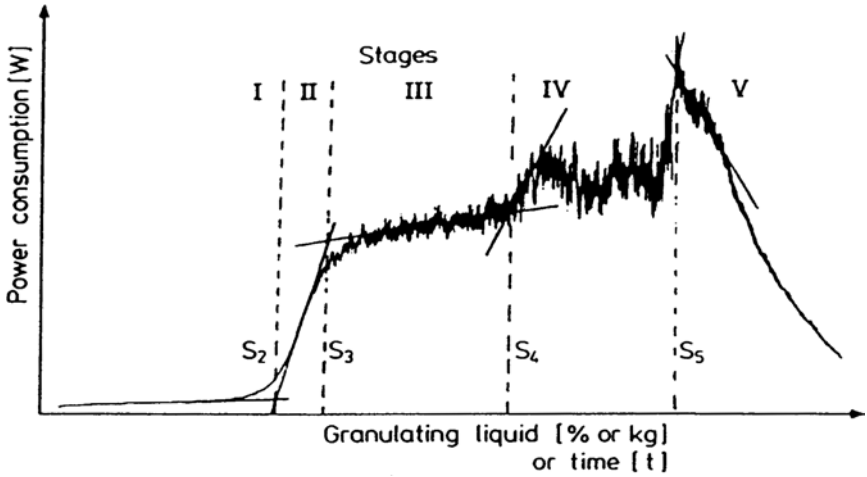

Figure 2 Division of a power consumption curve. *Source*: From Ref. 8.

The batch size ranged from 3.75 up to 60 kg. To obtain precise scale-up measurements, the excipients which were used belonged to identical lots of primary material [10% (W/W) corn starch, 4% (W/W) polyvinylpyrrolidone as binder, and 86% (W/W) lactose]. As can be seen from Figure 4, the amount of granulating liquid is linearly dependent on the batch size. During the scale-up exercise, the rate of addition of the granulation liquid was enhanced in proportion to the larger batch size. Thus the power profile, which was plotted

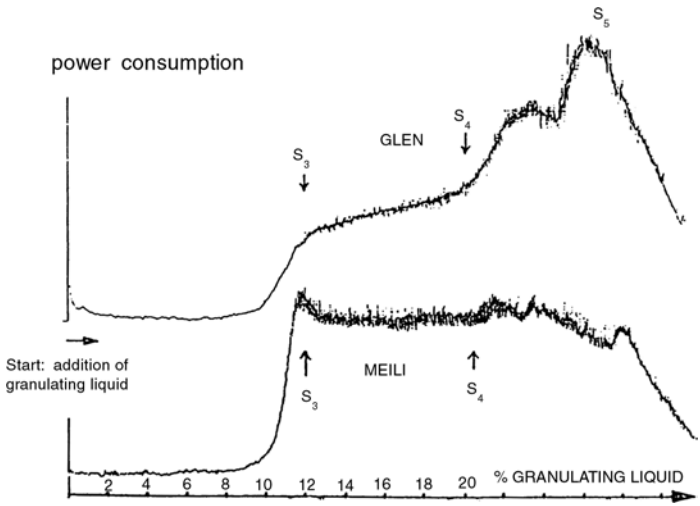

Figure 3 Power consumption profiles of two types of a mixer/kneader.

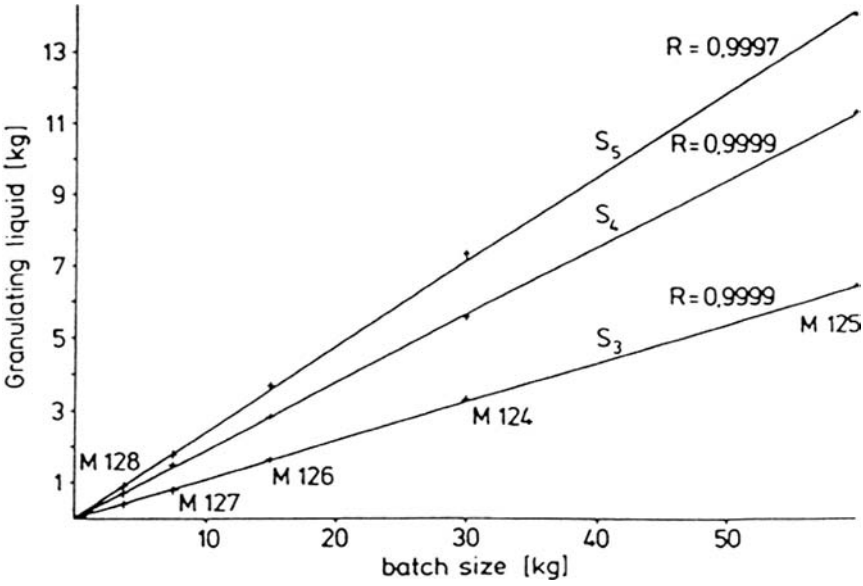

Figure 4 Scale-up precision measurements with identical charges. *Source*: From Ref. 6.

on the chart recorder, showed the characteristic S_3, S_4, and S_5—values independent of batch size within the same amount of time since the start of the addition of granulation liquid. This fact is not surprising as, in terms of scale-up theory, the functional dependencies of the dimensionless group numbers ~ 1 and ~ 2 were measured:

$$\pi = F(\pi_2) \tag{6}$$

The other numbers π_3, π_4, π_5, were kept essentially constant. From these findings, one can conclude that the correct amount of granulating liquid per amount of particles to be granulated is a scale-up invariable (6–9). It is necessary, however, to mention that during this scale-up exercise only a low-viscous granulating liquid was used. The exact behavior of a granulation process using high-viscous binders and different batch sizes is unknown. It is evident that the first derivative of the power consumption curve is a scale-up invariant that can be used as an in-process control and for a fine tuning of the correct amount of granulating liquid (Fig. 5).

Mechanistic Understanding of the Wet Agglomeration Process and the Power Consumption Profile

The following statements refer to the situation where a well-soluble binder is added in a dry state or where the binder is dissolved in the granulating

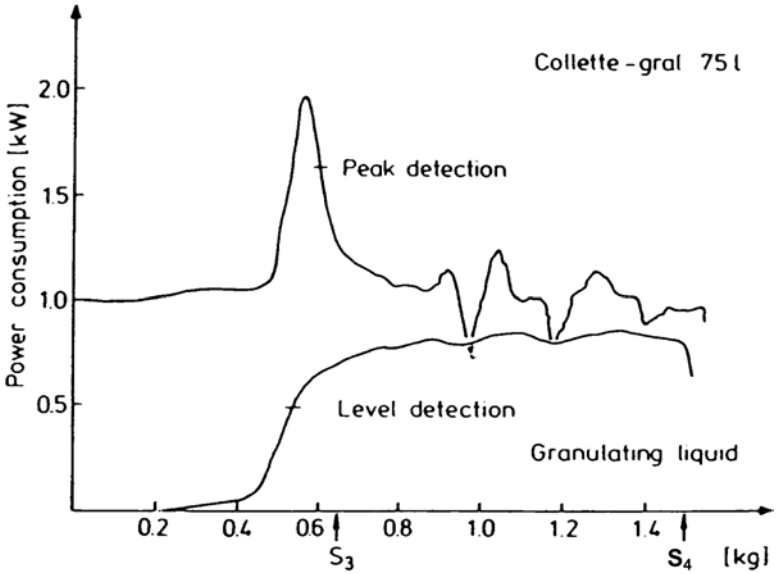

Figure 5 Power consumption profile of a high-speed mixer (Collette-Gral 751) with peak and level detection. *Source*: From Ref. 8.

liquid, showing a low viscosity. Due to environmental protection and other issues such as preferred wettability with water, a high-interfacial tension, distilled, or demineralized water is the granulating liquid of choice. As modern mixers/granulators are today often instrumented to measure the power consumption during the moist agglomeration process, emphasis is put on the interpretation of power consumption profiles and on the experiences obtained so far with this method. For a better understanding of the power consumption profiles, the following theoretical considerations are a prerequisite.

Liquid Bridge Force and Cohesive Stress

According to models described by Rumpf (21) and by Newitt and Conway-Jones (22), the cohesive forces that operate during the moist agglomeration process result from liquid bridges that are formed in the void space between the solid particles. The strength of the cohesive stress σ_c depends on the surface tension γ of the granulating liquid, the wetting angle δ, the distance a between the particles and the particle diameter x. In an idealized situation with $a = 0$ (contact) and $\delta = 0°$, the cohesive stress σ_c of the powder bed, consisting of isometric spherical particles with diameter x, where the void space is only partly filled up with granulating liquid (degree S^* of

saturation < approx. 0.3) is equal to:

$$\sigma_c = \frac{1-\varepsilon}{\varepsilon}\frac{A\pi\gamma}{x\{1+tg(\theta/2)\}} \tag{7}$$

with ε = porosity of the powder mass, A^* = proportionality constant, depending on the geometry of packing of the particles.

Tensile strength of moist agglomeration, i.e., green granules: Due to the principle of action = reaction, the cohesive strength σ_c is equal to the tensile strength σ_t of the moist particulate matter. The tensile strength σ_t of limestone particles with diameter $x = 71\,\mu m$ forming a powder mass with the porosity $\varepsilon = 0.415$ was measured as a function of liquid saturation S^* by Schubert (23), illustrating the relationship between σ_t and S^* for lower and higher degree S^* of saturation (Fig. 6).

In a first approximation the specific power consumption per unit volume dN/dV of the moist powder in a mixer is equal to:

$$dN/dV = \mu\sigma_c K \tag{8}$$

with μ as the apparent friction coefficient, σ_c the cohesive strength of the moist powder bed, K as the shear rate.

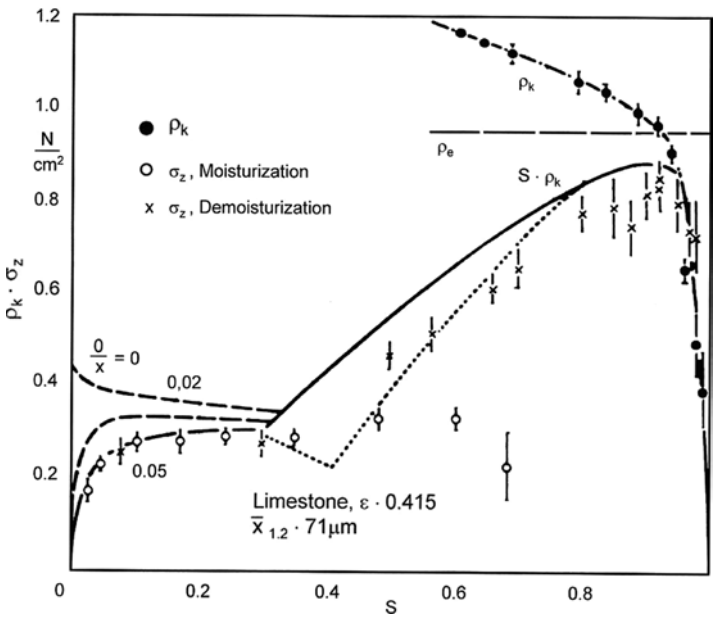

Figure 6 Tensile strength σ_t of a limestone powder bed as a function of the liquid saturation S^* of the void space between the particles. *Source*: From Ref. 23.

For a fixed coefficient of friction μ and a fixed dimensionless shear rate K, the measurement of the power consumption per unit volume of the moist powder mass is proportional to the cohesive stress σ_c. Thus, if the granulating liquid is added to the powder mass at a constant rate, the power consumption profile describes in a first approximation the cohesive stress σ_c as a function of the relative saturation S^* of the void space between the particles (Fig. 5).

The Use of Power Consumption Method in Dosage Form Design

Robust formulations are today an absolute prerequisite. Concerning the production of granules, the granule size distribution should not vary from batch to batch. The reduction of the variability of important product properties is the key issue of the FDA's Process Analytical Technology (PAT) initiative. This initiative is a challenge for the pharmaceutical industry and for academia (24). The key factors of the granulation process in a high-shear mixer are the correct amount and the type of granulating liquid. The interpretation of the power consumption method can be very important for an optimal selection of the type of granulating liquid. The possible variation of the initial particle size distribution of the active substance and/or excipients can be compensated in case of an intelligent in-process control method, e.g., based on the power consumption profile (Fig. 2). However, the formulation may not be very robust if the volume-to-volume ratio of certain excipients, such as maize starch and lactose, corresponds to a critical ratio or percolation threshold.

With dosage form design, it is often necessary to compare the performance of two different granule formulations. These two formulations differ in composition and, as a consequence, vary also in the amount of granulating liquid required.

Thus, the following question arises: how can the quantity of granulating liquid be adjusted to achieve a correct comparison?

The answer is not too difficult, as it is based on identified physical principles. A correct comparison between two formulations is often a prerequisite, as the dissolution process of the active substance in the final granulate or tablet can be affected both by the amount of granulating liquid and the qualitative change (excipients) in the formulation. In order to calculate corresponding, i.e., similar amounts of granulating liquid in different compositions, it is necessary to introduce a dimensionless amount of granulating liquid π. This amount π can be defined as degree of saturation of the interparticulate void space between the solid material (Fig. 2).

$$\pi = \frac{S - S_2}{S_5 - S_2} \tag{9}$$

Table 1 Physical Characteristics of the Starting Material

	Lactose	Corn starch
Bulk density (g/cm^3)	0.58	0.49
Tapped density (g/cm^3)	0.84	0.65
True density (g/cm^3)	1.54	1.5
S_m mass specific surface (cm^2/g)	3055	–
Mean diameter (μm)	40	25

where S is the amount of granulating liquid (in liters), S_2 is the amount of granulating liquid (in liters) necessary which corresponds to a moisture equilibrium at approx. 100% relative humidity, S_5 is the complete saturation of interparticulate void space before a slurry is formed (amount in liters).

Power consumption is used as an analytical tool to define S values for different compositions. Thus, the granule formation and granule size distribution of a binary mixture of excipients are analyzed as a function of the dimensionless amount of granulating liquid π. This strategy allows an unbiased study of the growth kinetics of granules consisting of a single substance, or binary mixture of excipients. Thus, it is important to realize that the properties of the granule batches are analyzed as a function of the dimensionless amount of granulating liquid (8,25–30).

Materials

The physical characteristics of the starting materials are compiled in Table 1. Polyvinylpyrrolidone was added in a dry state to the powder mix of lactose and corn starch at a level of 3% (w/w). As a granulating liquid, demineralized water was used and pumped to the powder mix at a constant rate of 15 g/min/Kg.

Methods

The principle of power consumption method was described in detail in theô publications (8,25–30). As a high-shear mixer, a Diosna V 10 was used, keeping constant impeller (270 rpm) and chopper speed (3000 rpm) during the experiments.

In order to reduce the possible effects of friability or second agglomeration during a drying process in dish dryers, on the granule size distribution as a function of the amount of granulating liquid added, the granules are dried for 3–5 minutes in a fluidized bed (Glatt Uniglatt) and subsequently for 15–25 minutes in a dish dryer to obtain moisture equilibrium corresponding to 50% relative humidity of the air at ambient temperature (20°C). The particle size distributions were determined according to DIN 4188, using ISO-norm sieve sizes (27).

The Myth of the Granulation End-Point

The manufacturing of granules or granulation process is still poorly understood, especially in cases where the necessary boundary conditions for an optimal granulation process are not fulfilled: Problems can arise if the granulating liquid (1) is non-Newtonian, and/or (2) dissolves an important amount of the powder formulation, and/or (3) if a hydration process, or (4) due to a higher temperature, a gelation process occurs. In an ideal case, the only function of the granulating liquid is to form liquid bridges between the particles for the granulation process.

The influence of the amount of liquid present in the granular material (% saturation) on power consumption and tensile strength measurements at different steps during the agglomeration process is shown in Figure 7. The maxima of power consumption were determined at 100% saturation, whereas the maxima of tensile strength measurements occurs at 90% saturation as expected (21,9). The tensile strength expresses the cohesiveness between the powder particles, which is dependent on saturation and capillary pressure. The measured tensile strength $\sigma(N/m^2)$ is equal to the volume specific cohesion (J/m^3). The obtained results proved that the power consumption measurement is an alternative, simple, and inexpensive method to determine the cohesion of powder particles.

Thus, if the cohesivity of the moist powder mass is monitored, e.g., by torque or power consumption measurement, a typical profile (Fig. 8) is

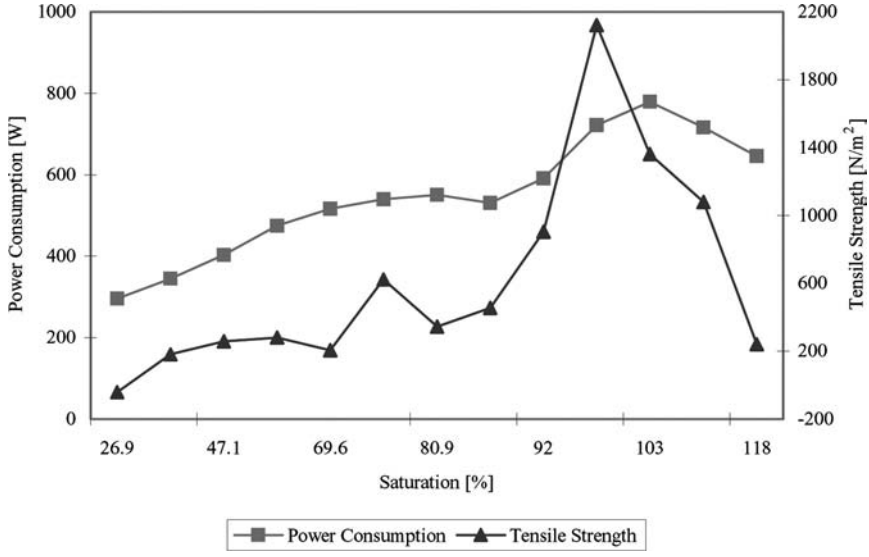

Figure 7 Comparison of power consumption and tensile strength measurements.

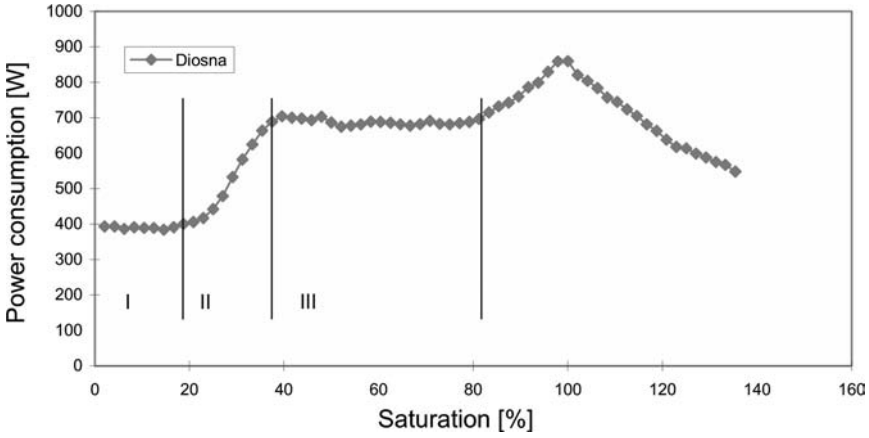

Figure 8 Power consumption profile of the high-shear mixer Diosna.

obtained (31,32). Figure 8 shows the power consumption profile for a composition with 86% (w/w) lactose 200 mesh, 4% (w/w) polyvinylpyrrolidon (as a binder in a dry state in the powder mixture, the only component which will be completely dissolved) and 10% (w/w) corn starch. The granulating liquid is demineralized water, which is added by a pump with constant speed.

The different phases can be easily interpreted: (I) water uptake by corn starch, (II) start of formation of liquid bridges, (III) filling up of the interparticular void space by the granulating liquid. Granules with a reproducible granule size distribution can be manufactured for amounts of granulating liquid, which correspond to a well-defined point of the plateau (see also the semi-logarithmic plot of the mean granule size in Figure 10 as a function of granulating liquid added). There is no granulation end-point; however, there is a possibility to control the granulation process by the detection of the steepest ascent in the power consumption profile (level or peak-detection method, Figure 5) and adding a constant amount of liquid. As an alternative, the inflexion point of the S-shaped curve of the power consumption profile can be determined for this ''fine-tuning'' process (14,29). The peak in Figure 5 describes a certain cohesiveness of the moistened powder bed at the beginning of the plateau phase. The peak (first derivative of the power consumption curve) is a signal provided by the powder mass and has a self-correcting property as the signal appears at an earlier time for a slightly coarser starting material, and later for a slightly finer material, and taking into account the initial moisture content of the primary material, which depends on seasonal effects.

In this respect, the automated controlled mode leads to a higher homogeneity of the granule size distribution (Table 2) than in the case of adding

Table 2 Yield and Size Distribution of Granules After a Manual and Automatic Granulation

Type of mode	Yield (% w/w) 90–710 μm	% Undersize <710 μm	Undersize <90 μm
Manual mode $n = 20$ batches	81.03 ± 2.42	88.30 ± 2.05	6.80 ± 0.51
Automatic mode $n = 18$ batches	91.45 ± 0.36	96.80 ± 0.31	5.40 ± 0.35

Source: From Ref. 9.

manually a predetermined constant amount of granulating liquid. Thus, the variability of the yield could be reduced by understanding the process.

Some Hints Concerning the Wet Agglomeration Process in a High-Shear Mixer to Avoid Problems

Granulation is often considered as much an art as it is a complex process. The following hints should be helpful to reduce problems.

The production of granules consists of the following steps in general:

1. Dry blending of the primary powder material, i.e., active substance and auxiliary substances in a mixer. Preference should be given to demineralized water as granulating liquid and the excipients and the drug should show relatively low water solubility with the exception of the binder. The binder should be preferably added in a dry state as part of the powder components.
2. For disagglomeration of cohesive fine powder or for security reasons (e.g., screws left in?), a sieving step should be included. Thus, for an optimal homogeneity of the powder mix, it is important to apply the following rule: Blending, Sieving, and Blending. It is evident that an appropriate mixer equipment should be used, such as a high-shear mixer. In the case of a very potent drug, the content of the drug is low and it is necessary to use micronized drug particles.
3. Wetting of the particles by adding granulating liquid, preferably pure water. If the binder is dissolved in the granulating liquid, the binder solution should be Newtonian, i.e., should show a low viscosity. It has to be kept in mind that the fine tuning of the amount of granulating liquid, which is optimal, can only be done if the binder is part of the dry premix. Thus, in modern high-shear mixers, the required amount of granulating liquid is often pumped into the mixer at a continuous constant rate. In order to avoid an overwetting of the powder mass, a power consumption profile should be measured. In an optimal case, i.e., if the formulation

is suitable, the power consumption profile can be used to control the amount of the granulating liquid which is necessary (Fig. 8)

4. Depending on the formulation and on the properties of the components in the powder it may be necessary to mass the moistened powder for some time before screening. However, it has to be checked as to whether the massing process can be avoided if the granulating liquid is pumped into the powder bed at a reasonable rate.
5. Final drying step: After the screening step, which may in certain cases have narrowed the original native granule size distribution, the granules may be preferably dried in a fluidized bed equipment, using, e.g., a temperature end-point of the granulate temperature to define the final moisture content (Chap. 7). Depending on the properties of the dried material, a final screening operation may be necessary.

ROBUST FORMULATIONS AND DOSAGE FORM DESIGN

The Effect of Percolation Theory

In the case of binary mixtures consisting of different substances, which, individually, may have a considerable effect on the physical properties (e.g., electrical conductivity) of the final product (granules, tablets, etc.), the ratio of components is essential. Thus, with a mixture between Al_2O_3 (an electrically insulating material) and copper powder, electrical conductivity of the Al_2O_3/copper tablet is only observed if the copper powder forms an electrical pathway between the electrodes attached to the surface of the tablet produced. The critical ratio where conductivity is measured corresponds to the so-called percolation threshold p_c (10). In the case of a fixed normalized amount π of granulating liquid, it is interesting to note that the granules obtained from a lactose/corn starch powder mixture lead to granule size distributions equivalent either to the granule size distribution of lactose or corn starch. This result can be interpreted on the basis of percolation theory (Fig. 9), i.e., that the properties differ for compositions below or above a critical ratio p_c of components between lactose and corn starch.

A QUASI-CONTINUOUS GRANULATION AND DRYING PROCESS (QCGDP) TO AVOID SCALE-UP PROBLEMS

Continuous Processes and the Batch Concept

In the food and chemical industry, continuous production lines play an important role, whereas the pharmaceutical industry production is mainly based on a batch type procedure. Concerning the safety of a dosage form

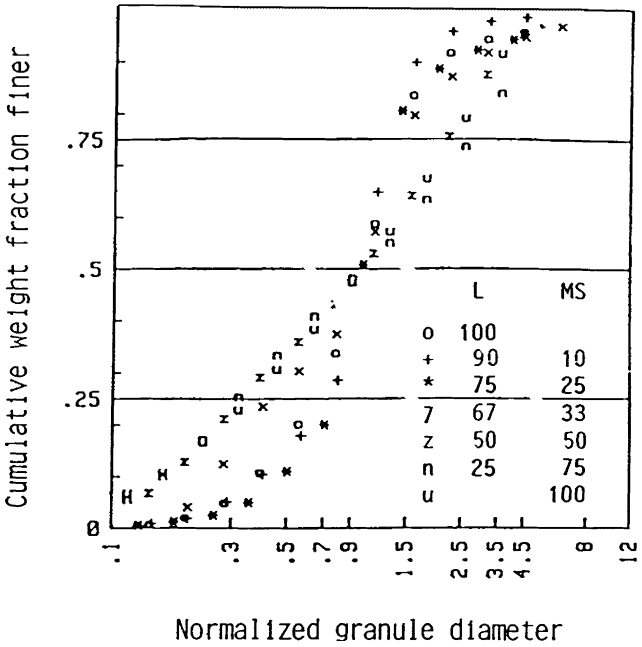

Figure 9 Cumulative particle size distribution of the agglomerates at a fixed normalized amount π (= 0.62) of granulating liquid for different ratios of the binary powder mixture lactose/corn starch.

and quality assurance, the batch concept is very convenient. Thus, a well-defined batch can be accepted or rejected.

In the case of a continuous process, a batch has to be defined somehow artificially, i.e., the amount of product—the amount of granules produced within six to eight hours. On the other hand, continuous processes offer two important advantages: (1) there is no difficult scale-up exercise necessary for larger "batches," and (2) a 24-hour automatic production line should be possible.

Development of the Quasi-Continuous Production Line for Granules

In order to combine the advantages of a batch type and continuous production, a prototype for a quasi-continuous production line was developed (15–18,33–35). The principle of this quasi-continuous production line is based on a semi-continuous production of mini-batches in a specially designed high-shear mixer/granulator which is connected to a continuous multicell-fluidized (Glatt Multicell®) bed dryer (Fig. 10).

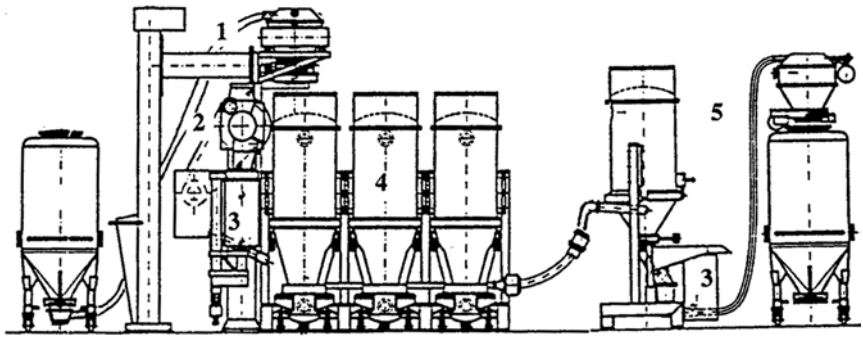

Figure 10 A quasi-continuous production line for granules with three drying cells. *Source*: Courtesy of Glatt AG, CH-4133 Pratteln.

In order to study the feasibility of such a quasi-continuous production line, different formulations were tested and compared with a conventional batch process.

The weighing system which is available on the market was not involved in the first experiments. Thus, a prefixed amount of powder of the placebo formulation was added to the specially designed high-shear mixer and thoroughly mixed. Subsequently, this amount of powder is granulated by continuously adding granulating liquid up to a fixed amount. The ideal amount of granulating can be defined according to the results of a power consumption measurement (6–9,29,30). Afterwards, the moist granules are discharged through a screen into the first cell of the multicell-fluidized bed dryer unit to avoid any formation of lumps. Thus, the quasi-continuous production of granules can be described as a train of mini batches passing like parcels through the compartments of dry mixing, granulation, and drying. The multicell dryer consists, in general, of three cells which are designed for different air temperatures, i.e., in the first cell, the granules are dried at a high temperature, e.g., 60°C, and in the last cell, ambient air temperature and humidity can be used to achieve equilibrium conditions. If appropriate, more cells can be added.

Due to this principle, a batch B defined for quality control purposes consists of a fixed number of n mini batches (subunits), i.e., B=nb.Thus, a tight in-process control of the mixing/granulation (6–9) and drying step (14) provides an excellent "batch" record of the quasi-continuous production of granules and an excellent opportunity for a continuous validation of the process and the equipment (14–18,32–34).

Thus, based on the positive results obtained with the thesis work of Schade (15) and Dörr (17), a new plant for quasi-continuous wet granulation and multiple-chambered fluid-bed drying was developed by Glatt AG CH-Pratteln in cooperation with F. Hoffmann-La Roche Ltd. Basel and the Institute of Pharmaceutical Technology of the University of Basel.

For this achievement, the Institute of Pharmaceutical Technology received the Innovation Award of the Cantons Basel-City and Basel-Country in 1994.

The system gives a new possibility for industrial manufacturing and Galenical development of pharmaceutical solids specialties and has, following purposes:

Automatized unattended production, withdrawing from scale-up experiments and, thus, a shorter development time for new specialties, with the aim of a shorter time to market. Manufacturing procedures can be simplified, validated faster, and the quality of granules, tablets and kernels, compared to common production, is equal or better. Different solids specialties have been tested and validated.

Goals of the Quasi-Continuous Granulation and Drying Line

Unattended production: One of the general aims of quasi-continuous granulation and fluid-bed drying is unattended production. The production of small subunits of 7–9 kg, instead of a whole batch, allows an automatized, iterative granulation and drying procedure. The division of the process into different compartments (mixing, sieving, and drying compartments) guarantees the reproducibility of the Galenical properties of each subunit.

No necessity for scale-up experiments: The granulation and drying of subunits of 7–9 kg, instead of a whole batch, gives the possibility to use the plant for laboratory and production scale, because the batch size is no longer characterized by the machine size, but by the number of produced subunits. Using the same plant in Galenical research, development and production may shorten the time to market for new solids specialties.

Simplification of manufacturing procedures: Existing manufacturing procedures can be taken over from common equipment without changing components. In certain cases, it is possible to simplify the procedures. The small mixer size and the geometry of the mixing elements allow the addition of the binders into the premixture and granulation just with water.

Identical or better quality of granules and tablets: The quality of the produced granules and tablets has to be equal or better and fulfills the product specifications.

Results

Constant values and reproducibility of the process are important facts of quasi-continuous granulation. The tests also show equal or better quality of granules and tablets, compared to common granulation equipment (Diosna~ P-600 high-speed granulator).

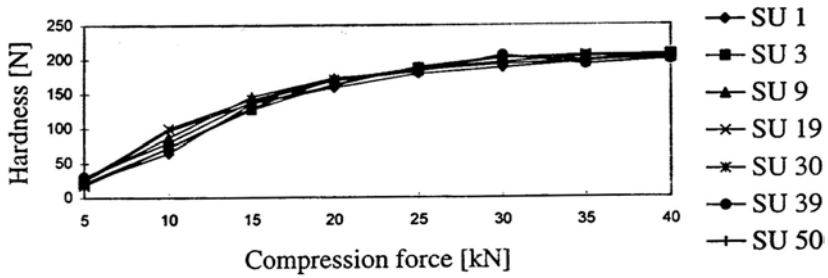

Figure 11 Compression force/hardness profile (Formulation 1).

Compression force/hardness profile: The compression/hardness profile of a granule batch is an important property. Different subunits of two formulations were selected and compressed using different compression forces in order to obtain tablets. The tablets were tested for hardness as a function of different subunit numbers (Figs. 11,12). From experience, it is well known that certain formulations show an excellent compression profile as small batches but do not keep this property on the batch size increasing . This is another advantage of the quasi-continuous production concept as, in principle, the quality of the small batch is not changed by the repetitive procedure.

Description of the Production Plant

The Glatt-Multicell unit for quasi-continuous granulation and fluid-bed drying consists of the following elements: a transport and dosage system for mixer filling (1), a horizontal high-speed plough-share mixer (subunits of 4–9 kg of premixture can be granulated) with an airless spray pump for the granulation liquid (2), rotary sieving machines for wet and final sieving (3), a three-chambered fluid bed dryer for predrying, final drying and cooling down to room temperature (4), a transport system to collect the granulated subunits in a container (5), and an integrated washing-in-place system (Figs. 13,14).

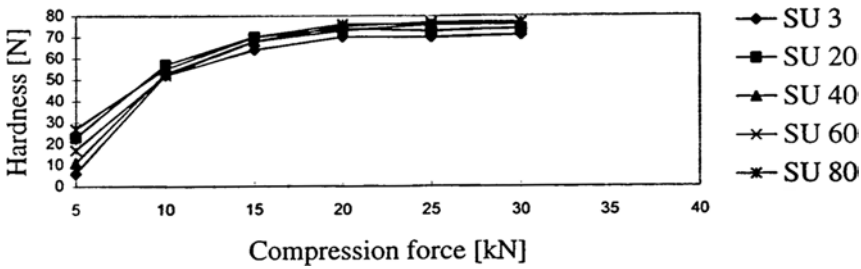

Figure 12 Compression force/hardness profile (Formulation 2).

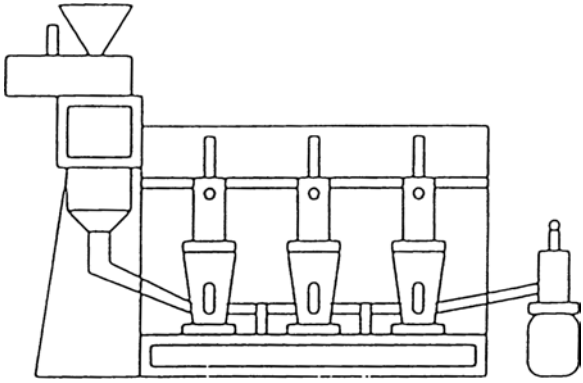

Figure 13 Layout of the Glatt-Multicell.

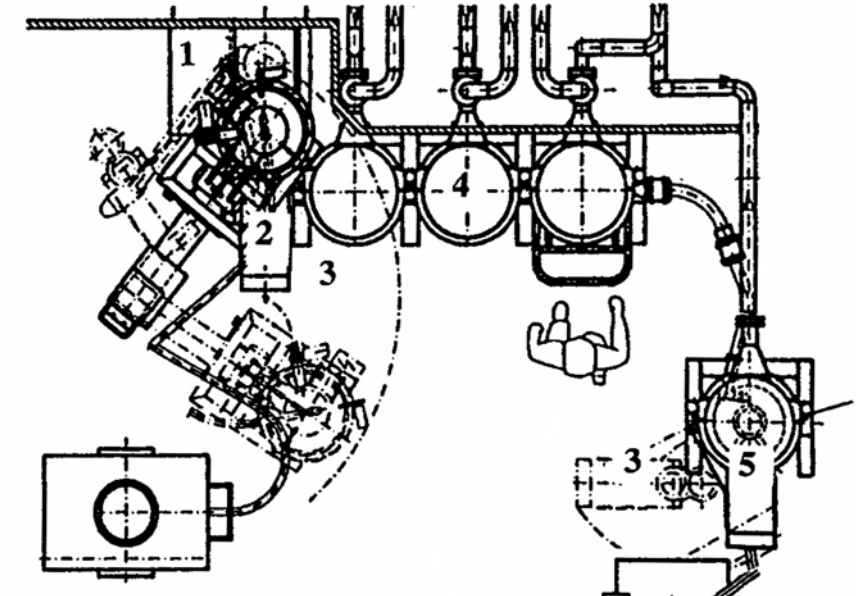

Figure 14 Top view of the Glatt-Multicell.

Advantages of the Quasi-Continuous Granulation and Drying Line

The production line can be fully automated and equipped with a cleaning-in-place (CIP) system. The moist agglomeration process can be monitored for each subunit by power consumption in process control device. Due to the three different cells of the Glatt Multicell drying equipment, a gentle drying of temperature, sensitive drug substances is possible. According to necessity, a "Just in time—production" of the desired batch size B can be implemented. Early, small-sized batches can be already considered as production batches of identical quality. Thus, these early batches can be put on a long-term stability test already at the beginning of the development of the dosage form. As the early clinical batches are produced on the exact same equipment as the large production batches, no bioequivalence test between early clinical batches and later production batches is needed. Due to these facts, no scale-up development is necessary. Thus, the development time and the time needed to market can be reduced. Last, but not least, it has to be kept in mind that the major problem consists in the fact that the formulation is optimized on small-scale equipment but is, for obvious reasons, no longer optimal for large-scale equipment.

To take advantage of such a concept, it is absolutely important that such equipment, i.e., identical equipment, is available in the R&D and in the manufacturing department.

SCALE-UP OF THE CONVENTIONAL FLUIDIZED BED SPRAY GRANULATION PROCESS

Introduction

The batch type fluidized bed process is widely used in the pharmaceutical industry for spray granulation and/or drying as a step subsequent to some type of wet granulation. Batches produced in high- or low-shear granulators, or by the fluidized bed spray granulation process, may be dried rapidly owing to the superior heat and mass transfer capabilities of this technique. Granules produced by the wet granulation methods (high and low shear) and by fluidized bed spray granulation typically differ in structure and, possibly, behavior. The force applied and the absence of evaporation during high-shear granulation tend to produce denser granules. The fluidized bed is a low-shear process in which granule properties are determined by process parameters, and the resulting granules are porous. The two processes generally do not produce equivalent products, and, in most cases, product formulations may need to be adapted to the chosen method. In high-shear granulation, the list of process variables is comparatively short—main impeller configuration and speed; chopper speed; liquid addition method and droplet size (if atomized); and, finally, kneading time and power consumption or torque for end-point determination. The list is considerably longer in fluidized bed

spray granulation and will be elucidated later. Although there are many process variables, and there is interaction among them, in general, they are well understood and repeatable. Batch type fluid bed equipment is tailored to batch size, which may range from a few 100 to more than one metric ton. The combination of reproducibility and batch size flexibility results in a highly efficient manufacturing method.

Equipment Considerations

Figure 15 shows a fluidized bed dryer vertically integrated with a high-shear granulator, a wet mill, bottom discharge, and a dry mill. The basic components of the machine will be described, beginning with the entrance of the

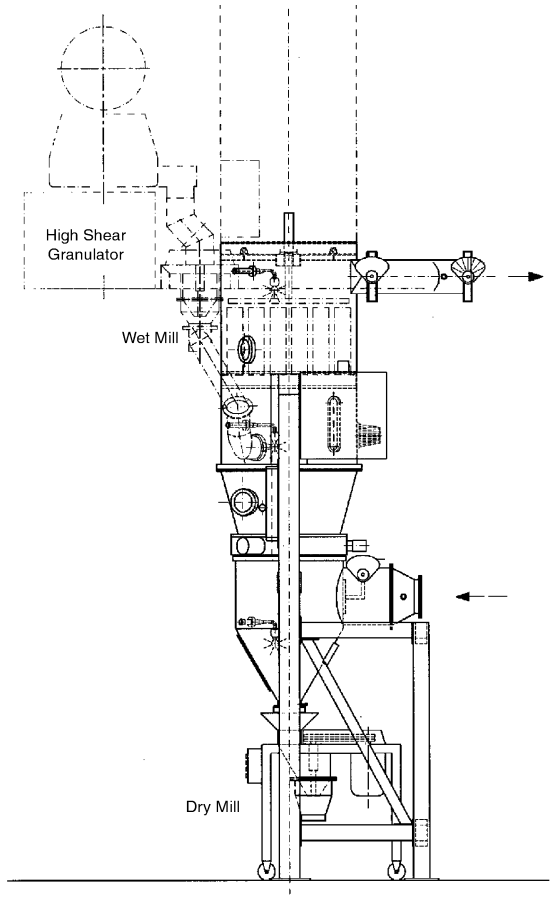

Figure 15 Fluid bed dryer with integrated high-shear granulator and mills.

process air. The lower plenum acts as a transition piece, conducting the process air from the round duct from the air handler (where the air is heated and may be humidity controlled) to the bottom of the product container. Within this region, a probe is located for measuring the temperature of the incoming process air. The plenum is typically open, but may contain components for an agitator, which may be used for types of products which are resistant to only moving by the air stream.

The product container itself is conical to enhance mixing and allow a high velocity to be used where the air enters the product bed. The base of the product container is multi-purpose. Typically, a perforated plate acts as an air distribution device to assist the air which enters the lower plenum at a right angle to the product container, to spread evenly across the bottom of the product bed. Above the distributor plate, there is a fine screen which acts as a product retention device. The type and porosity of this screen may be product-dependent. The most porous screens are those defined in the A.S.T.M.E.-11 specification (used in the U.S. Standard or Tyler series). The openings are roughly square, with the number per linear inch specified. With a defined wire diameter, the size of the opening is then identified (for example, a 100 mesh screen has 100 openings per inch which are 150 μm). An advantage is that this type of screen is very porous (high percentage of open area) and not as subject to occlusion as other types of screening. A potential disadvantage is that it is thin and hence comparatively weak, and the square opening does not allow retention of relatively fine material (with a possibility of product loss in the lower plenum). For this reason, a more commonly used type is referred to as a Dutch Weave screen. This variety has the wires tightly packed in one direction, creating openings which are a more tortuous path for the product to travel through to the lower plenum. The porosity of this screen is referred to in microns, and this may be the dimension of the longest portion of the opening. For instance, a 150 μm Dutch Weave screen would have an opening of 150 μm in one direction with the other dimension equal to the diameter of the wire. This results in a screen with better product retention characteristics, but lower permeability (which is not necessarily a problem). These screens are also stronger, and as such, have a longer life in a manufacturing operation.

The use of screens for product retention in fluidized bed driers is not universal. In some applications, both product retention and air distribution are handled by a low permeability perforated sheet or plate which contains relatively small openings. In the gill plate or Conidur® sheet, high-fluidization air velocity through the plate may be sufficient to avoid significant material loss into the lower plenum, in spite of the fact that it is likely that some of the product is finer than the openings in the distributor plate. This type of plate may be more commonly used in applications where CIP (for product change) or wash-in-place (WIP) (a somewhat less stringent

requirement) is considered in the machine design. In some plate designs, the perforations impart a horizontal flow to the air and product. The distributor plate is a composite of directed flow segments, which may be used in conjunction with side discharge. When processing is completed, the product is withdrawn (with vacuum assistance) through an opening at the perimeter of the product container. The directional nature of air flow is not manifested during processing. However, as the batch is evacuated and the bed depth decreases, the residual material begins to rotate in the product container. As it approaches the opening, it is drawn out into a receiving vessel.

Other components may be housed in the product container. First, product temperature is often a critical control parameter for the spray granulation and/or drying process. A temperature probe is located in the product container, such that it is in contact with the flowing product. Within a short distance above the base of the product container, heat is exchanged for moisture, and evaporative cooling depresses the product temperature to a value well below the inlet air temperature. Above this critical distance, the bed may be considered to be isothermal—the rapid motion of material creates a condition whereby the temperature is the same throughout a large region due to the rapidly fluidizing batch. As such, the location of the product temperature probe is not critical. It may be placed in an area above the product container, in the lower segment of the expansion chamber. Provided that the product continues to wash over it, the temperature response will be a consequence of conduction (solid to solid contact), not convection, which is a slower process, and therefore less responsive.

Another common component is a device for withdrawing a product sample during the process for monitoring product attributes, such as particle size (and distribution), density, and most importantly, moisture. There is debate as to how representative the sample is, and its reliability may be product-dependent. If particle size distribution in the drying granulation is reasonable, it is a good method of in-process monitoring, and its use is strongly encouraged.

Moisture-laden air exits the batch, passing through a filter (sock-type fabric or a type of cartridge). A third temperature probe may be located in the exhaust duct of the machine, measuring the exiting air temperature. At some distance from the product itself, it measures exit air temperature, which may be subject to heat loss to the surrounding metal mass. Also, the change in temperature is the result of convection, and the consequence is that it is likely to be less responsive than the product temperature probe—it reacts more slowly and to a lesser degree, due to the fact that it is not in direct contact with the solid product. It is therefore suggested that the exhaust temperature be used only as a backup to the product temperature probe, especially if the temperature is used to aid in the moisture end-point determination.

Table 3 Major and Minor Process Variables to Be Considered in Fluidized Bed Spray Granulation

Major	Minor
Inlet air temperature	Nozzle port size
Inlet air volume	Nozzle height (with respect to static bed surface)
Inlet air dew point	Nozzle spray cone angle
Product/exhaust temperatures (dependent variables)	Spray liquid temperature (viscosity)
Solution spray rate	Outlet filter type
Product moisture content during spraying (dependent variable)	Outlet filter shake (pulse) interval/time
Atomizing air volume/pressure	
Batch size	

Process Variables

Table 3 lists variables to be considered when developing the fluidized bed spray granulation process. As shown in Table 3, the variables are typically divided into two categories—major: those typically expected to significantly influence product properties; minor: those that will have minimal impact. There are also interactions between variables. The major variables can be divided into two significant categories: those impacting the drying rate (inlet air temperature, volume, and dew point), and spraying (solution spray rate and atomizing air volume/pressure). For instance, process air volume affects not only the amount of heat energy delivered to the bed, but also the fluidization pattern and particle velocity. Spray rate affects not only the droplet size (and the resultant granule size), but also the product moisture profile during spraying. When basic feasibility studies have been conducted, it is recommended that the list be narrowed, and that further experiments be carried out within the context of a design of experiments (DOE) to quantify their impact on the properties of the finished product. The domain for the process variables must be selected carefully to assure that the resulting effects are measurable. The success of scale-up from the lab to the manufacturing equipment strongly depends on the robustness of the product and process, as well as a good understanding of which variables have the greatest impact in small-scale machines.

Scale-Up Considerations

Planning for scale-up is already a part of the development process. A formulation which is a challenge to produce or reproduce in the laboratory will be an even larger problem in manufacturing equipment. In production, batch

size will increase substantially, and there will be a consequential mass effect. Fluidized bed granules or agglomerates are by nature porous, and there are both surface and interstitial pores. These generally enhance compressibility, disintegration and dissolution. However, porosity and tensile strength are inversely related, and the influence of mass with respect to the larger batch size is such that compaction may reduce porosity and/or enhance attrition (loss of granule structure). It is understandable that a larger batch size and increased bed depth influence the granules. Granules in a batch of 500 kg are exposed to considerably more force than those in a laboratory scale batch of 5 kg. Although the magnitude of the impact is probably not predictable, in general, an increase in bulk density of approximately 20% as a function of scale-up in large machines may be expected. However, another key granule property, particle size and distribution, is related to droplet size, and as long as this is preserved in scale-up, the granule size and distribution of the larger batch should be comparable.

Scale-Up Considerations: Drying-Process Air Volume

Irrespective of the method used to produce the granules and the consequent batch size, a significant factor in scale-up is the increase in drying capacity in larger equipment. The heat delivered to the bed of fluidizing granules comes from a combination of inlet air temperature and volume, and, to a lesser extent, inlet air dew point. As previously mentioned, the process air volume is also responsible for fluidization behavior, and this will be the first variable to be considered.

All products require a volume and velocity of air to break the cohesive bonds between particles, wet, or dry, and to permit the batch to become fully fluidized. Laboratory trials will yield values for process air volume for the various stages of the process. Using this volume and the dimensions of the product container, a ''face'' velocity through the distributor plate can be estimated (permeability of the plate is not considered). It is reasonable to assume that approximately the same velocity will be needed in scale-up. In Table 4, estimates for process air volume are derived from the cross-sectional areas of the base of the product container for various sizes of fluid bed dryers.

The derived values for process air volume in Table 4 should be used as starting points in larger equipment, and adjusted depending on the observed fluidization behavior and performance of the outlet air filter (excessive pneumatic transport of fines into the filter may affect the ability to maintain the process air volume). Other factors may influence the response of the product. Larger product containers may be geometrically similar, and reasonably preserve the aspect ratio of the batch (bed depth to diameter) in order to permit axial (vertical) rotation or mixing of the fluidizing particles. Products which consist of materials which are coarse in particle size (large substrates or granules for drying) or are high in density will

Table 4 Estimations of Process Air Volume in Scale-Up as a Function of Product Container Distributor Plate Dimensions

Machine Model	GPCG-5	GPCG-60	GPCG-300
Product container volume	22 L	220 L	1,060 L
Cross-sectional area of bottom screen	0.042 m^2	0.42 m^2	1.04 m^2
Velocity of air through bottom screen	1.0 m/sec	1.0 m/sec	1.0 m/sec
Volume of air required to maintain velocity	151 m^3/hr[a]	1,512 m^3/hr	3,744 m^3/hr

[a]Assume that this value was determined by experimentation, and that the velocity (above) was calculated using bottom screen or distributor plate cross-sectional area. Values for process air volume in the remaining product containers are estimates based on maintaining the same face velocity.
Source: Equipment dimensions courtesy Glatt Air Techniques, Inc.

react strongly to the increased bed depth common in manufacturing equipment. If the bed depth is excessive, bubbles of air will have difficulty in making their way through the mass. They will coalesce into very large bubbles, and this may result in slugging, where a large mass of product emerges from the bed as a unit before collapsing back into the product container. This fluidization regime is generally considered to be undesirable. While this behavior may be inconsequential to a drying process, it is unwelcome for spray granulation because of the adverse influence on droplet distribution in the bed. A second consequence of an overly deep bed is that the product container wall is conical, and viscose product may not funnel downward at the wall, resulting in regional bed stalling. In this condition, a significant quantity of wet product remains at the wall, unable to be exposed to the heated process air for drying. Moisture distribution uniformity will be compromised, as will finished product properties. On the machine control panel, fluidization behavior may be seen in the response of the product differential pressure—a smoothly fluidized bed will yield a narrow range from peak to trough, whereas a slugging bed will reveal broad swings from the average. For purposes of illustration, the example in Figure 16 shows the evolution of fluidization behavior in a top spray fluidized bed layering and coating process where a large quantity of solid material is applied. As both the batch size and the particle size of the product increase, the range (peak to trough values) in product differential pressure is broader. The early stages of the process illustrate the behavior of a batch with a comparatively shallow bed depth, and the latter stages indicate the behavior of a considerably deeper bed.

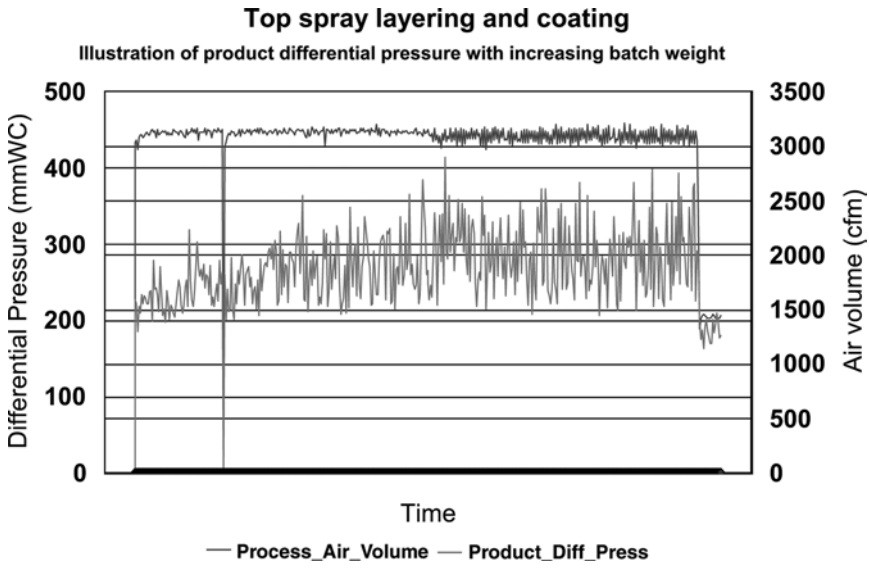

Figure 16 Influence of increasing batch size on product differential pressure and process air volume for a pilot scale top spray layering and coating process.

Scale-Up Considerations: Drying-Process Air Dew Point and Dry Bulb Temperature

Prior to a discussion on the impact of processing air dew point and temperature on the drying rate behavior of a product, it is necessary to consider heat and mass transfer. Water will move from the granule to air in an attempt to reach an equilibrium, or saturated condition, determined by thermodynamics, which can be read from a phase diagram or psychrometric chart. The rate at which water will move from liquid in the granule to vapor in the air increases the further away the system is from equilibrium. When the water evaporates, it requires an amount of energy, the heat of vaporization, in order to change from liquid to vapor. Because of this, we must also consider transfer of heat as well as movement of material. These concepts can be described by equations shown in Table 5.

It is obvious that changes in the driving force change the rate at which material and heat is removed. In addition, the proportionality constant is dependent on the surface area, temperature, drying air velocity, and the properties of the material, such as porosity, density, morphology, etc.

A major component in the delivery of heat energy to the product is the temperature of the process air. A lesser contributor, but one which should not be ignored, is the dew point of the air for processing. When warm air of a given moisture content (absolute humidity) interacts with a water-wetted

Table 5 Equations for Heat and Mass Transfer in a Wet Granule

Heat transfer	$\frac{\Delta Q}{\Delta t} = h(T_2 - T_1)$	Where: Q = Heat; t = Time; T_1 = Inlet air temperature; T_2 = Product temperature; h = Heat transfer coefficient; M = Mass; C_1 = Moisture in ambient air; C_2 = Capacity of the heated air; K = Mass transfer coefficient; H_{vap} = Heat of vaporization.
Mass transfer	$\frac{\Delta M}{\Delta t} = K(C_2 - C_1)$	
Relation between equations	$\frac{(\Delta Q/\Delta t)}{\Delta H_{vap}} = K(C_2 - C_1)$	

batch, the heat is exchanged for moisture, and the temperature of the air drops (by evaporative cooling). The product temperature closely approximates this air temperature. If water moves freely within the substrate, the resulting temperature will represent a dew point. In other words, the air leaving the product and the machine tower is completely saturated with moisture, or is at 100% relative humidity.

If the process is developed such that a comparatively low incoming air temperature is used, variations in incoming air humidity may dramatically impact both the product temperature and the drying rate. As an illustration, assume that the process air volume and liquid spray rate are held constant. In the first example, ambient air, with a dew point of 10°C, is heated to 60°C for processing. Assuming free movement of water in the substrate, air passing through the product bed will result in a product temperature of 26°C. From psychrometric software (Winmetrix v.4.5, Drying Doctor Inc., Verdun, Quebec, Canada), the incoming air contains 7.62 g of water per kg of dry air. Exchange of heat for moisture results in 21.22 g of water per kg of dry air in the exiting air stream, for a net drying rate of 13.60 g/kg. The temperature difference between the inlet and product (60–26°C) is 34°C, and reflects a moderate drying rate. In the second example, the only change is the ambient air dew point, now elevated to 20°C. When heated to the process air temperature set point of 60°C and passed through the bed of wet product, the air again leaves saturated, containing 26.89 g of water per kg of dry air, but at a product temperature of 29.8°C. Nearly a 4°C rise in the product temperature is the consequence of reduced evaporative cooling

due to the increased absolute humidity in the ambient air (14.68 g/kg at 20°C dew point versus 7.68 g/kg at 10°C dew point). The smaller difference between the inlet and the product temperatures (60°–29.8°C) of 30.2°C is reflective of a decreased drying rate. In real terms, the drying rate is 12.21 g/kg in the second example and 13.60 g/kg for the first scenario, for a difference of 1.39 g/kg or 11.4%. In a simple drying application, this translates to a longer drying time when the ambient air is more humid. However, if spray granulation is taking place, there is a larger concern. In most processes, the spray rate is held at a fixed value. In this set of examples, there would be a significant difference in wetting rate, or the rate at which the batch accumulates moisture. At the higher dew point, the batch would accumulate moisture faster, and would have a higher moisture profile for the entire batch, particularly at the end of spraying. If granule properties are related to this moisture profile, which is a common characteristic, it is evident that the product could be significantly impacted simply by the variation in ambient air dew point when using a relatively low inlet air temperature.

Dew point of the process air is a concern in scale-up. In small laboratory machines (up to about 2 kg in batch capacity), the air for processing may be drawn from the room in which it is being operated. A facility air handling system typically controls the humidity of the lab areas in a comparatively narrow range throughout the year, in absolute and relative terms. In a sense, it is tantamount to having humidity control on the fluid bed. However, larger machines (pilot, production scale) require increased air volumes and must draw their air from outside of the building, making their processes subject to seasonal variation in ambient humidity. The aforementioned problem may be addressed in a number of ways. First, high inlet air temperatures should be explored, because very hot air has a much greater capacity for water. Repeating the previous examples with the process air temperature elevated to 90°C will illustrate the point. Ambient air with a 10°C dew point, heated to 90°C and passed through a bed of wet product will yield a product and exit air temperature of 32.1°C. The exit air will contain 30.68 g water per kg of dry air, and subtracting the 7.62 g/kg initial absolute humidity, will yield a drying rate of 23.06 g/kg. Ambient air with a 20°C dew point, heated to 90°C and passed through a bed of wet product will yield a product and exit air temperature of 35.1°C. In this case, the exit air will contain 36.80 g water per kg of dry air. Subtracting the 14.70 g/kg absolute humidity in the ambient air yields a drying rate of 22.10 g/kg, a difference of 0.94 g/kg, or only 4.1%. It is evident that there will still be an impact of the variation in ambient air dew point, but the magnitude is considerably smaller.

Ideally, all sizes of the fluid bed equipment should be equipped with inlet air dew point control. In the northern climates, this would include dehumidification in the summer months and humidification during the cold, dry winter months. In this manner, the inlet air dew point becomes a recipe

managed set point, and there is no seasonal influence of ambient dew point, irrespective of the selected inlet air temperature (high or low).

Irrespective of the possibility of dew point control, high inlet temperatures should be explored because of the influence on productivity (considerably shorter process times). Additionally, a high inlet air temperature may help to counter a factor typically only seen in scale-up: the so-called "mass effect," or the influence of the weight of the larger batch size on itself. Fluidization of a heavy batch may cause compaction of the porous granules, as mentioned previously. In general, granule porosity is related to temperature—the higher the temperature, the greater the porosity, and the lower the resulting tensile strength. This influence is critical for products requiring rapid dispersibility characteristics in their end use—those packaged into sachets and intended to be stirred into water before use, for instance. If laboratory experimentation has found that the process air temperature strongly impacts product properties, it is advisable to use the same value in scale-up. However, if compaction in the larger machine causes an increase in density (lower porosity), and the porosity was a desirable product attribute, to an extent, a higher inlet air temperature may offset the mass effect seen in the production scale equipment. A second benefit is the probability that the moisture content during spraying may be very close to the desired residual maximum value, essentially eliminating a drying step. Once spraying is completed, the process is stopped and the batch immediately discharged.

Scale-Up Considerations: Spraying-Spray Rate and Droplet Size of Sprayed Liquids

A major consideration in the scale-up of a fluidized bed spray granulation process relates to liquid delivery. As stated previously, granule size and structure are strongly related to droplet size of the binder or water being sprayed into the fluidizing substrate particles. It is imperative that the larger equipment is capable of delivering the liquid to the bed at a rate which is compatible with the available drying capacity, and at a droplet size which is essentially equivalent to that used in the laboratory. In other words, if the spray rate in the laboratory was 100 g/min at 200 m^3/hr process air volume, and the production equipment operated at 4000 m^3/hr, the starting point for spraying in the production equipment would be 2000 g/min, or a rate equal to 20 times that used in the laboratory machine, irrespective of batch size.

The spray nozzle (or nozzles) in the production machine would need to be of a size such that this increased spray rate is within its performance envelope (similar droplet size, uniform in distribution), or equivalence in granule size would be impossible. Figure 17 illustrates the concept that atomizing air pressure must be adjusted to attain similar average droplet sizes in all three scales of process equipment at the desired spray rate (data from

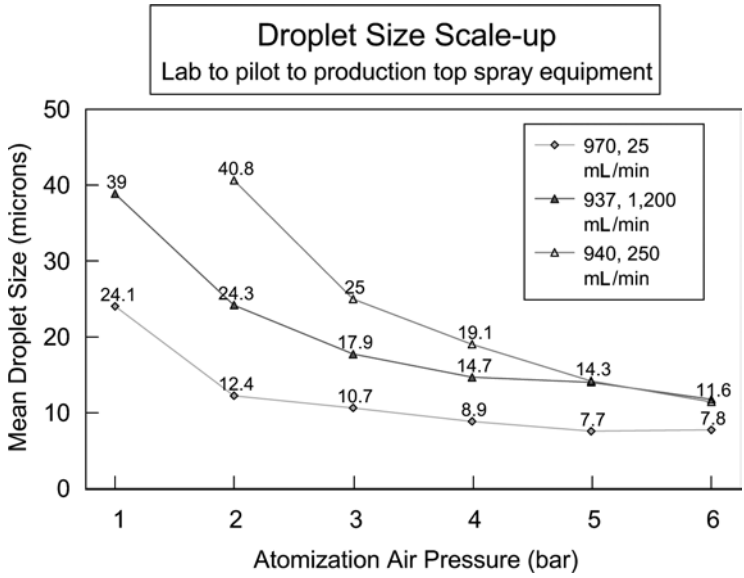

Figure 17 Average droplet sizes as a function of spray nozzle type (lab, pilot, and production), spray rate and atomizing air pressure.

Düsen-Schlick, GmbH, Dresden, Germany). The 970 series is typically found in laboratory inserts, the 940 series, also a single-headed nozzle, is used in pilot scale machines, and the 937 is a three-headed nozzle, typically fitted in production equipment. In very large machines, multiple wands may be used with several multi-headed nozzles to spread the liquid over as much of the fluidizing product bed surface area as possible (typically to improve productivity).

The three different nozzles have slight differences in the configuration of the liquid insert and air cap (the path for the atomizing air), but the largest difference is in the size of the annulus between these components to permit the higher volume of compressed air to flow at the same atomizing pressures for atomization of the liquid stream (Fig. 18).

Scale-Up Considerations: Product Moisture Content During Spraying

In combination with the drying rate (inlet temperature, volume, and dew point), the spray rate influences the rate of moisture build-up in the batch. In the example shown in Figure 19, the water addition rate exceeds the drying rate; the binder itself has an affinity for moisture, and is building in the product bed; and granule size is increasing with time. The change in slope begins at the 60-minute time point, when a slight increase in process air volume is enacted

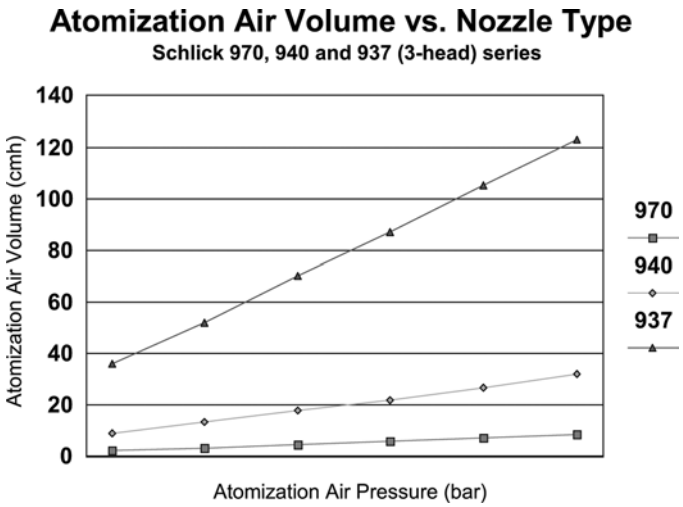

Figure 18 Atomizing air volume and nozzle type for laboratory, pilot, and production scale nozzles.

to ensure that the bed remains fully fluidized as it increases in weight and granule size. The rapid rate of moisture loss, beginning at the 105-minute data point, is due to an increase in the inlet air temperature for drying. This moisture profile was developed in small scale equipment, and the example shown is for a large production batch. Product attributes, such as granule size and

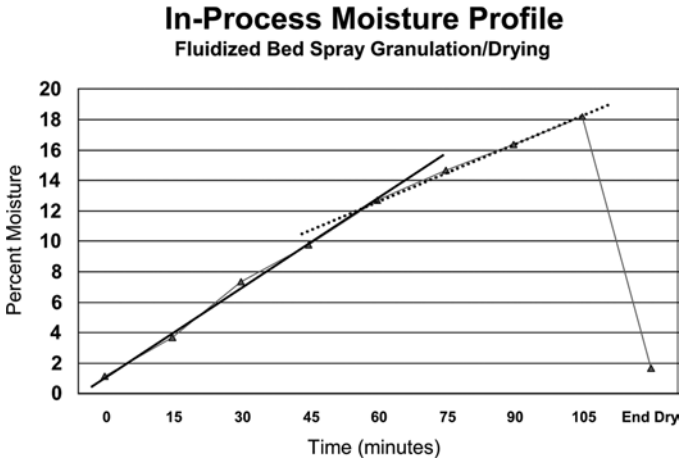

Figure 19 Representative in-process moisture profile for a fluidized bed spray granulation.

distribution bulk densities, and tablet properties, such as hardness, friability, and disintegration time, are reproduced when this moisture profile is duplicated in routine manufacture.

Scale-Up Considerations: Minor Process Variables

The list of minor process variables includes several items with respect to the spray nozzle (port size, nozzle height above the static bed surface and the spray cone angle). Figure 20 shows the relationship between nozzle port size and spray rate for a three-headed production scale nozzle. With a typical atomizing air pressure operating range of two to five bar, it can be seen that the port size has almost no influence on droplet size, except for the high-spray rate and small port size combination. Even at four bar and above, again, there is no influence. It is recommended that nozzle port size be selected based on the viscosity of the liquid to be sprayed.

Low-viscose liquids can use small ports, and thicker solutions somewhat larger orifices to allow some back pressure to build in the spray nozzle. In this manner, if a port should become clogged, increasing the spray rate through the remaining ports, the total liquid line pressure will rise. An operator can intervene to correct the problem before the larger droplet size results in an increased granule size.

Droplet size is also typically impacted by liquid viscosity. In general, viscose liquids produce large droplets, resulting in coarse granules. In the case where the binder solution viscosity varies with temperature, the liquid

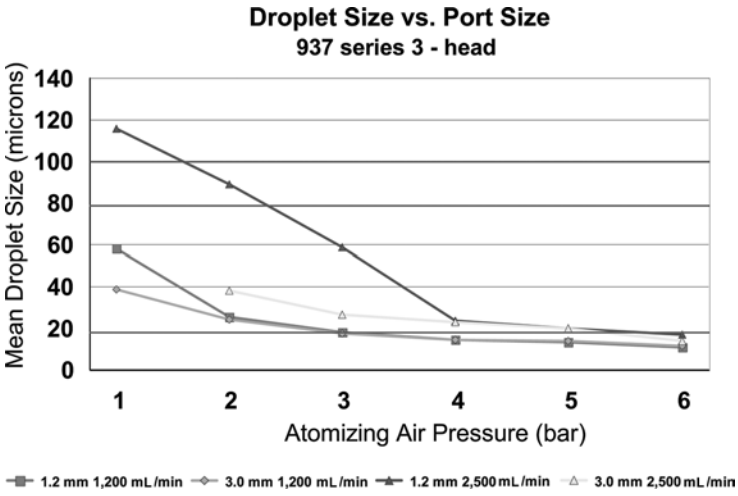

Figure 20 Droplet size as a function of 1.2 mm and 3.0 mm nozzle ports; spray rates of 1200 and 2500 mL/min using water.

temperature must be controlled in order that viscosity and droplet size can be reasonably reproduced.

Nozzle height above the static bed and the (spray pattern) cone angle impact the zone of contact between the droplets and the fluidizing substrate. In general, the maximum contact volume is desired (spreading the droplets over the largest product bed surface area). Experimentation has shown that this typically results in a narrow granule size distribution by minimizing the possibility of a locally high droplet/moisture concentration. In practical terms, this relates to adjusting the nozzle cone angle to its largest value. In lab and pilot scale nozzles, this is adjustable—in production nozzles, it is fixed. Nozzle height above the static is the only way to impact the contact area in large equipment. In many spray granulation applications, the process air leaving the product bed is at or near saturation; therefore, spray drying of the binder material with the spray nozzle mounted well above the static bed is not a concern.

As mentioned previously, process air volume is selected based on material properties. Fine materials are easily transported above the product bed into the outlet air filter. If the process air volume and velocity are excessive, material will be retained in the filters. Fines may become imbedded in the filter material, causing high pressure and a resultant loss in air volume. Filter selection is based on two criteria—porosity (the size of the pores in the fabric) and permeability (the number of openings per unit area). Filters are often selected with a porosity value that matches the particle size of the unprocessed substrate materials. In general, small porosity yields reduced permeability. The practical implications are that low permeability requires reduced process air volume, and this may impact productivity. Periodically, materials collected in the filters should be returned to the bed. This is accomplished by shaking the filters. Contemporary equipment which has a split filter housing should have each filter half shaken at least every 30 seconds, such that building filter pressure does not interfere with control of process air volume, a key parameter. If the machine is constructed with cartridge type filters, the filter ''pulse'' should be frequent, such that the fines are returned to the product bed to be exposed to the spray liquid.

SUMMARY

Batch type fluidized bed processing is widely used in the pharmaceutical industry. Mass effects and drying capacity are key concerns in scale-up for drying of granulations produced in the separate steps of high- or low-shear granulation. A broad range of process variables exist in the fluidized bed spray granulation process and some may have a significant impact on product properties. Experimentation should be conducted at the laboratory scale to determine the robustness of the formulation and process so that scale-up activities result in a product with equivalent performance.

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9

Roller Compaction Scale-Up

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PROLOGUE

This is both a new subject and chapter to the Second Edition of *Pharmaceutical Process Scale-Up*. Some elements of this chapter were described in the first edition of the *Handbook of Pharmaceutical Granulation Technology*, in the chapter titled Roller Compaction Technology, by the lead author in 1997 (1). A number of new equipment design features, research, roller compaction usage in the industry, and new technology advances have added to the best practices of roller compaction within the pharmaceutical unit operation in our industry. The interested reader will have to wait for a comprehensive book (in process at this time) to link numerous journal articles, chapters, and investigative works for technology completeness. This chapter serves the abbreviated purpose of defining roller compaction scale-up in the pharmaceutical industry.

SCALE-UP BACKGROUND

In the aforementioned chapter in the First Edition Reference 1, I mentioned, "There is no such thing as a standard approach to solve compactor scale-up or compactor equipment changes in the pharmaceutical production process" (1). At that time of the publication, it appeared that was very much the case history of roller compaction scale-up in the pharmaceutical industry. This understanding was based on the fact that there were no pharmaceutical industrial journal articles published at the time on the subject. On the other hand, it was also true that considerations, approaches, and examples presented in that chapter were experienced by others and were not all-inclusive.

This new chapter does offer specific compaction process scale-up and equipment technology transfer concepts observed by the author and others that were published since Reference 1. To those who contributed to and continue to advance roller compaction technology, it is gratifying to see a paradigm shift and an expansion to dry granulation roller compaction technology in our industry. Additionally, with process analytical technology tools, significant opportunities to standardize roller compaction scale-up exist, and will be discussed later in this chapter. Our view is that process analytical technology tools will drive roller compaction scale-up for years to come with the work established by Gupta and others.

Factors in scaling-up a pharmaceutical compaction process or equipment technology transfer involve a number of issues and technologies. Numerous considerations go beyond the specific process and technology that evolve from the pilot plant to the manufacturing technical operations center. Most of these concerns are centered on the plant's current operations, and its previous use or manufacture of dry granulations using roller compaction technology. (See Reference 2 that cites a comparative study summary.)

Some scaling factors that go beyond specific formulation technical aspects follow. What type of equipment manufacturer support is expected? What are the reputation and reliability of the equipment manufacturer in the country where the start-up will occur? What is the equipment manufacturer's customer service record worldwide? How many days will it take to replace a broken or worn out part? Does the equipment manufacturer carry a reliable stock parts inventory? A survey evaluated industrial practices and preferences that addressed some of these questions (2).

Additionally, what is a company's commitment to technology and engineering support before and after start-up? Who provides the training costs? Who pays what? Are the in-process testing equipment and necessary analytical equipment operational, qualified, and ready when needed? Who will perform the validation requirements (equipment and process)? These are some of the key questions and concerns that go beyond the hardware issues and technology that must be addressed prior to the project start-up.

Discussing, planning, and financing these issues with the receiving site's key personnel, equipment vendors, and research, development, engineering, and technology personnel well in advance of the technology scale-up will make for a much more successful process technology transition and transfer. Are the technical experts prepared and available to provide the timely support both vendor and technology? Have the following equipment, support systems, and process condition questions been asked and answered: What? Where? Why? When? How? and Who? A scale-up evaluation checklist referring to personnel training, logistical matters, engineering support, raw material delivery system, compactor design, environmental issues, raw material characterization is referenced for the interested reader (1).

Professionals in pharmaceutical manufacturing science understand that no single written journal article could hope to provide universal guidance on roller compaction scale-up. On the one hand, the best way to solve these types of challenges is to attack them systematically. This usually can be achieved through appropriate process qualifications and validation efforts: trial and error approaches before start-up, knowledge of equipment processing capabilities and limitations, and understanding raw material's variability. On the other hand, process analytical technology tools and approaches will offer different pathways to attack the scale-up and the validation process (3).

Discussion about roller compaction solid dosage form scale-up in this chapter does not imply compliance with suggested scale-up and postapproval change (SUPAC) guidelines. The described approaches do not necessarily provide ideas/recommendations that meet tests and filing requirements for changes in manufacturing processes and equipment. Scale-up guidance for immediate-release solid dosage forms and postapproval changes have been published. We suggest that readers familiarize themselves with the referenced material (4).

Even as this chapter is crafted, the Food and Drug administration's Center for Drug Evaluation and Research (CDER) has issued significant new changes for good manufacturing practices for process validation when advanced pharmaceutical, science and engineering principles, and manufacturing control technologies provide a high level of process understanding and control capability (5). The Agency indicates that manufacturers using such procedures and controls may not necessarily have to manufacture multiple conformance batches to complete process validation (5). How times are changing!

SCALE-UP TECHNICAL ILLUSTRATIONS

The following roller compaction scale-up examples illustrate technology strategies that identify equipment design features, process parameters, and evaluations defining roller compaction scale-up processes.

Carver Press Scale-Up to Roller Compactor

Gereg and Capolla developed process parameters determined by a model laboratory bench scale Carver press, model C (Carver Inc. Savannah, Georgia, U.S.A.), which were translated to production scale compactor parameters (6). Their study provided a method to predict whether a material is suitable for roller compaction. Their study objectives were to characterize properties of the material to identify process parameters suitable to achieve the necessary particle size and density using the dry granulation process and then translate laboratory information to a production scale roller compactor. Actually, information developed from a Carver press was correlated and scaled-up to a production scale Fitzpatrick roller compactor, Model IR 520 (Fitzpatrick Co., Elmhurst, Illinois, U.S.A.) The compactor produced very similar powder granule characteristics as the Carver press. Various lactose materials, available as lactose monohydrate or spray dried lactose monohydrate, were used as the model compounds. Results indicated that a parametric correlation could be made between the laboratory bench Carver press and the production scale compactor, and that many process parameters can be transferred directly.

Using the Carver press, samples were compressed by applying a force from 500 to 10,000 lb in increments of 500 lb. The compact volume, density and pressure were calculated. The scientists prepared regular-grade lactose compacts using the Fitzpatrick compactor from conditions determined from the Carver press. The selected compaction force value was converted to the total compaction force by multiplying the surface area of a compact by the selected compaction pressure using Equation (1).

$$F = P \times A \tag{1}$$

where F is the total force between rolls, P the selected pressure, and A the compact surface area. The total compaction force was applied to the roller compactor by converting it to pound-force per linear-inch of roll width, and ultimately converted to hydraulic pressure using the Fitzpatrick conversion table (6).

The roller compactor's full axial rolls produced compacts in the form of "sticks." The unmilled compacts from both machines had the same density, $1.3\,g/cm^3$. The milled roller compacts produced comparative granules except for bulk density and correspondingly the Carr index values:

$$(\text{Tapped density} - \text{Bulk density}) \div \text{Tapped density} \times 100\,\%$$

The milled compacts generated slightly larger particles where the round slugs produced from the Carver press produced a greater number of fines. The compactor flow rate for the milled roller compacted material was twice as fast as that of the Carver press' granules, but both flow rates were deemed acceptable. The authors concluded that both methods produced, for all practical purposes, equivalent granulated material.

Slugging Vs. Compaction Technology

A new antibiotic tablet was introduced internationally in three countries. Two countries did not have compactors to manufacture the product. Their process consisted of the following unit operations:

- Blend ingredients
- Mill blend
- Blend milled ingredients
- Slug blend
- Size slugs
- Blend ingredients
- Compress final granulation

In the third country, roller compaction was substituted for the slugging process. While the sizing of the slugs and compacts were completed on different machines, and the particle size results were not exactly the same in each situation, the tablet content uniformity results were equivalent. Content uniformity relative standard deviations of 1.5–2.0% ($n = 10$ tablets) were routinely achieved. The tablet dissolution profiles averaged 95% or higher within 30 minutes in each country.

The success in manufacturing the tablet formulation (with varying batch sizes of 250–900 kg) and achieving reproducible tablet physical results was due in part to the robustness of the formulation design and the active drug's compressibility characteristics. Illustration of the different particle size distributions observed and equipment parameters employed to achieve the desired results are noted in Tables 1 to 3 (1).

VACUUM DEAERATION EQUIPMENT DESIGN EVALUATION

Pilot compaction trials were conducted to investigate the vacuum deaeration effect when compacting an antibiotic powder with 0.2 g/cm^3 density. The

Table 1 Granulometry of Powder Blends Manufactured Using Slugging Technology in Country 1

	Mesh size (% retained accumulated)					
Lot no.	#80	#100	#140	#300	#325	Pan
1	59	64	71	78	84	100
2	51	57	65	73	82	100
3	57	62	69	74	79	100

Note: Slugging parameters: 4 ton pressure, 0.75 in flat faced tooling, slug weight = 0.8–1.0 gr, slug hardness, = 12–18 Strong Cobb units, sized through oscillator #16 mesh screen.

Table 2 Granulometry of Powder Blends Manufactured Using Slugging Technology in Country 2

	Mesh size (% retained accumulated)					
Lot no.	#20	#40	#60	#100	#200	Pan
1	9	28	42	60	67	100
2	9	27	41	59	66	100
3	9	27	41	58	65	100

Note: Slugging parameters: 4 ton pressure, 0.75 in. flat faced tooling, slug weight = 0.8–1.0 gr, slug hardness, = 12–18 Strong Cobb units, sized through oscillator, #1.1 mm screen.

study determined the compact throughput, compact density, and fines (not compacted during vacuum deaeration) when using a new equipment feed system design. The parameters controlled and monitored during the compaction process were: vacuum deaeration pressure, roll pressure, roll and screw speeds, room temperature, and humidity.

The equipment feed design consisted of a funnel-shaped powder hopper (with no vacuum deaeration system) that was located directly above the rolls. The powder hopper was retrofitted with vacuum deaeration capability. A high compression feed screw, fitted inside the funnel hopper, fed the powder directly into knurled rolls. The compaction trials were conducted with and without vacuum deaeration. The compact was carefully collected directly on a #10-mesh screen. Powder particles, that were not compacted (i.e., those particles which were not attached to the compact, for example, fines bypassing roll compaction and the non-adhering compacted powder particles) were weighed and separated. The compact was not milled. The parameters are noted in Table 4.

The conclusions drawn from this trial indicated vacuum deaeration, employed in the described equipment design, increased the compaction rate, reduced the fines (non-compacted powder), and increased the compact density (R.W. Miller, unpublished notes, June 1996).

Table 3 Granulometry of Powder Blends Manufactured Using Slugging Technology in Country 3

	Mesh size (% retained accumulated)					
Lot no.	#20	#40	#60	#100	#200	Pan
1	23	51	63	73	80	100

Note: Compactor parameters: roll pressure = 62–65 bar, roll speed = 8 rpm, horizontal screw feed = 52 rpm, de-aeration = −0.2 bar, sized by double rotary granulators: #4 mm and 1.2 mm screens.

Table 4 Compactor Parameter Settings and Compact Physical Properties

Trial no.	Vacuum deaeration (15 in. Hg)	Roll pressure (kN)	Roll speed (rpm)	Screw speed (rpm)	Compact density (g/cm^3)	Compact rate (g/min)	Fines not compacted (%)
1	No	50	4.8	27	1.05	604	7.1
2	No	50	6.8	98	1.07	1172	8.1
3	Yes	105	4.8	27	1.21	772	5.6
4	Yes	50	6.7	27	1.11	848	5.8
5	Yes	70	5.2	27	1.25	856	5.8

Wet Granulation Technology vs. Slugging Technology vs. Roller Compaction Technology

A highly water-soluble drug was incorporated at 35% into hard gelatin capsules. The active drug substance characteristics were described as: small needle-shaped particles, low bulk density, $\approx 0.1\ g/cm^3$, extremely poor flow, "sticky," and highly compressible.

Initially, a conventional wet granulation process was investigated but proved not feasible due to the high solubility of the active bulk drug. When granulating, pockets of highly wetted areas formed preventing uniform moisture distribution and granule formation. Additionally, granulating with a solution of the drug was not acceptable because the amorphous form of the compound developed after drying.

Based on the encountered difficulties during the wet granulation process, the formulation scientists developed a dry slugging granulation process. This process had some deficiencies. For example, it was difficult to compress slugs to a similar consistency because of the extremely low bulk density and poor blend flow properties. Additionally, the weight and hardness of the slugs varied throughout the slugging powder process, and from batch to batch. This situation created a final blend batch-to-batch non-consistency in particle size distribution, bulk and tap densities (Table 5). Additionally, due to the extremely poor flowing powder blend, the process was not amenable to tablet scale-up; it took 10 hours to slug and size the 100 kg preblend.

Using the same active drug blend, 2×5 kg pilot compaction trials were conducted using an AW-120 (Alexanderwerk Inc., Horsham, Pennsylvania, U.S.A.). The compactor was fitted with deaeration capability. Results from numerous trials indicated batch-to-batch consistency in particle size distribution, bulk and tap densities (Table 6). The compaction process was scaled-up to a rate of 100–150 kg/hr using the same parameters as in the pilot trials. The granules manufactured from the compactor scale-up produced superior tablet physical properties compared to the slugging process (1). This example illustrates roller compaction technology delivering consistent and predictable powder properties compared to a slugging unit operation.

Table 5 Final Blend Physical Properties Manufactured by Slugging Process.

Lot no.	Mesh size (percent retained)							Bulk density (g/cm^3)	Tap density (g/cc^3)
	#30	#50	#80	#100	#120	#200	Pan		
N93C018C[a]	18.3	38.0	15.5	6.6	5.5	9.3	6.8	0.58	0.71
N93J071C[a]	15.8	30.0	17.1	7.1	6.2	10.9	12.8	0.56	0.72
N93M109C[a]	16.3	33.5	19.7	7.4	6.9	10.4	5.8	0.47	0.68
N94D053[a]	19.8	36.1	19.2	5.6	4.7	7.6	6.9	0.52	0.75
N94G101C[a]	8.9	40.9	19.7	6.2	4.4	8.9	11.0	0.60	0.87
N94H117C[a]	8.6	26.5	22.9	9.7	6.7	10.8	14.7	0.49	0.78
N95006[a]	11.7	31.2	19.9	8.4	5.8	8.7	14.3	0.58	0.81
N95008[a]	15.4	33.8	20.2	7.0	6.0	8.3	9.3	0.58	0.80
N95044[a]	13.6	35.5	22.4	8.9	5.7	8.8	5.1	0.51	0.73
N95134[a]	7.8	27.5	22.9	7.7	7.6	10.8	15.8	0.57	0.76

[a]Sized by oscillator equipped with #20 mesh screen.

Roller Compactor Pilot to Scale-Up Level

A roller compactor scale-up was conducted to show the effect of process scale-up on tablet robustness and predicted in vivo performance by Sheskey et al. (7). The effects of the scale-up from laboratory to pilot plant on granulation, tablet physical properties, and drug release of samples produced with roll compaction were compared with samples produced by direct compression. The study involved a formulation containing the model drug theophylline and hydroxyl-propyl methyl cellulose. The scale-up experimental protocol was established using the FDA's Guidance for Industry SUPAC-MR: Modified-Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls: In Vivo Dissolution Testing and In Vivo Bioequivalence Documentation (September 1997).

The TF-Mini and TF-156 compactors (Vector Corporation, Marion, Iowa, U.S.A.) were equipped with concavo-convex rolls and single flight screws. The roll speed of the TF-156 was scaled to achieve the same linear velocity 74.2 in./min as the TF-Mini model. This setting maintained a comparable dwell time for material in the compaction zone. The TF-156 roll force was scaled to 5.6 ton, which equaled a force per linear-inch approximately equal to the TF-Mini 3.1 ton/in. roll width. The authors established a feed screw speed to roll speed ratio of 1.3:1 for the trials. Table 7 gives the compactor equipment settings.

Compacts were milled and final blends were compressed into tablets (Table 8 gives resultant powder properties). Tablets were tested for friability, thickness, hardness, and drug release.

Results of roll compaction and milling trials indicated that there were insignificant differences between pilot and plant scaling. All laboratory and

Table 6 Physical Properties of Blends Manufactured Using Alexanderwerk AW-120 Roller Compactor

Lot no.	Screw speed (rpm)[a]	Roll pressure (bar)	Mesh size (% retained)							Bulk density (g/cm^3)	Tap density (g/cm^3)
			#30	#50	#80	#100	#120	#200	Pan		
1	45	62.5	19.4	39.9	14.0	5.7	3.8	5.7	11.4	0.60	0.69
2	38	62.5	18.8	43.2	12.9	5.2	3.3	3.9	12.6	0.60	0.72
3	38	50.0	14.2	41.2	16.2	6.3	3.9	3.4	14.8	0.60	0.72
4	38	75.0	15.1	42.2	16.1	5.8	3.5	3.8	13.5	0.60	0.70
5	30	62.5	11.6	37.7	16.2	6.8	4.2	1.7	21.8	0.60	0.72
6	53	62.5	12.6	40.6	17.4	7.0	4.4	1.5	16.5	0.58	0.70
7	38	62.5	16.4	40.7	15.2	5.4	3.6	1.6	17.2	0.58	0.71

[a]Roll speed and vacuum deaeration were kept constant at 8 rpm and 0.2 atmospheres, respectively. Roller compactor was equipped with 5 mm primary screen. Final sizing was conducted using an oscillator equipped with #20 mesh screen.

Table 7 Vector Freund Roller Compactor Equipment Settings

Trial parameters	1	2	3	4	5	6	7	8	9	10
Compactor TF models	Mini	Mini	156	156	156	156	156	156	156	156
Roll speed (rpm)	6	4	4	4	4	4	8	8	16	16
Throughput (kg/hr)	2	12	12	11	11	11	19	23	45	40
Linear roll velocity (in./min)	74.2	74.2	74.2	74.2	74.2	74.2	148.4	148.4	148.4	148.4
Screw speed (rpm)	17.9	5.2	5.2	5.2	5.2	5.2	10.4	10.4	20.8	20.8
Screw speed/roll speed (rpm)	3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1
Roll force (ton)	3	5.6	5.6	5.6	6.6	4.6	5.6	6.6	5.6	6.6
Force/linear inch (ton/in.)	3.1	3.1	3.2	3.2	3.8	2.7	3.2	3.8	3.2	3.8
Mill design	RI	RI	RB	RB	RB	RB	RB	RB	RB	RB
Granulator, U.S. Standard mesh screen	12	12	16	14	14	14	14	14	14	14
Granulator speed (rpm)	500	500	117	117	117	117	117	117	117	117

Abbreviations: RI, rotating impeller; RB, rotating bar; roll diameter and width, TF Mini: 100 mm × 25 mm; TF 156: 150 mm × 44 mm.
Source: Adapted from Ref. 7.

Table 8 Powder Properties from Non-Roller Compacted Formulation and Powder Properties from Vector Freund Lab and Pilot Roller Compaction Processes

Trial description	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compressibility index (%)
Original formulation (non-compacted)	0.415	0.645	36
Lab roll compaction 1	0.610	0.800	24
Pilot roll compaction 2	0.620	0.730	15
Trial 3	0.520	0.700	26
Trial 4	0.540	0.710	24
Trial 5	0.550	0.680	20
Trial 6	0.530	0.700	24
Trial 7	0.540	0.690	22
Trial 8	0.560	0.740	24
Trial 9	0.560	0.720	22
Trial 10	0.560	0.710	22

Source: Adapted from Ref. 7.

pilot roller compaction trials demonstrated improved powder flow ability in comparison to the non-roller-compacted original formulation (Table 8). The authors cited that all the tablets from roll compacted granulations exhibited strong physical properties, i.e., minimal chipping, no breaking, and no physical defects such as capping or lamination. Despite differences in tablet hardness and small differences in tablet properties, there were no significant differences in the rate of drug release among the direct compression ANDA product and the tablets produced by laboratory and pilot roller compactor processes. Roll compaction scaling did not affect in vitro drug release results (7).

Additional efforts by Sheskey et al. completed the scaling of their earlier work to a production scale compactor TF-3012 (Vector Corporation, Marion, Iowa, U.S.A.) (8). Table 9 shows the settings used to scale to the TF-3012. Like the TF-Mini and the TF-156, the TF-3012 was equipped with concavo-convex rolls, a single-flighted-feed-screw and no vacuum deaeration. Parameters from Table 7 Trial 7 were used to meet minimal feed screw speed requirements (4 rpm) to scale to the TF-3012 production machine. The roll force was scaled to 10.8 ton, which produced a force per linear inch similar to that used with the TF-156 (3.2/in. roll width). The feed screw speed was set at 5.2 rpm to maintain a ratio of feed screw speed to roll speed of 1.3:1, equal to that used with the TF-156. These ratios provided an adequate delivery of the model drug blend to the compaction zone. Also, the TF-3012 sizing granulator was comparable to the velocity used for the TF-156 milling process (rotor bar $\sim$ 107 ft/min).

Table 9 Vector Freund Roller Compactor Parameters from Continued Trials

Trials and parameters	11	12	13	14	15	16	17	18	19	20
Compactor TF model	3012	3012	3012	3012	3012	3012	3012	3012	3012	3012
Roll speed (rpm)	4	4	4	8	8	8	18.4	18.4	18.4	18.4
Throughput (kg/hr)	75	75	75	130	130	135	242	228	228	228
Linear roll velocity (in./min)	148.5	148.5	148.5	297	297	297	683	683	683	683
Screw speed (rpm)	5.2	5.2	5.2	10.4	10.4	10.4	23.4	23.4	23.4	23.4
Screw speed/ roll speed (rpm)	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1
Roll force (ton)	10.8	9.8	11.9	10.8	9.8	11.9	10.8	9.8	11.9	11.9
Force/linear inch (ton/in.)	3.1	2.8	3.4	3.1	2.8	3.4	3.1	2.8	3.4	3.4
Mill design	RB	RB	RB	RB	RB	RB	RB	RB	RB	RB
Granulator, US Standard mesh screen	14	14	14	14	14	14	14	14	14	14
Granulator speed (rpm)	87	87	87	87	87	87	87	87	87	87

Abbreviations: RB, rotating bar; roll diameter and width, TF 3012: 300 mm × 90 mm.
Source: Adapted from Ref. 8.

Results generally indicated that the TF-3012 trials exhibited reduced bulk density and increased compressibility index values compared to the TF-Mini and TF-156. The authors postulated that increased fines were caused from the milling operation, which may have occurred due to longer compact retention time in the mill chamber. All tablets manufactured from the compactors exhibited similar physical characteristics. Samples from the production-scale compactor trials showed faster drug release than did those from the laboratory compactor trials. Also, the pilot plant compactor trial f_2 statistics (see definition below) were always larger than >80, however, production scale compactor trial f_2 results were usually ~50, thus indicating some dissolution differences between small-scale versus large-scale roller compaction processing with the modified release matrix system studied (8):

$$f_2 = 50 \log\left\{\left[1 + 1/n_{t=1^n} \sum w_t (R_t - T_t)^2\right]^{-1/2} \times 100\right\} \quad (2)$$

where f_2 is defined as the similarity factor, w_t an optional weight factor, n the number of data points collected, and R_t and T_t the percent drug dissolved at each time point for the test and reference products, respectively (8).

Roller Compactor Development to Manufacturing Scale-Up Using Active and Placebo Blends

An initial narrow range of roller compaction parameters was established for an active 5% preblend granulation using an Alexanderwerk WP 50 roller compactor (150 × 75 mm roll dimensions, Alexanderwerk Inc., Horsham, Pennsylvania, U.S.A.) fitted with 4 mm and 1 mm granulating screens. No trend was noted with any of the measured parameters: ribbon thickness for all three granulations ranged from 1.35 to 1.44 mm. Recycling of material was not required, as there was no significant powder leakage around the rolls, and the fines (particles finer than 200-mesh) were <20% (Table 10).

Additional trials developed an expanded operational range for the 5% active preblend formulation. Parameters are identified in Table 11.

The strategy to scale-up the AW 50 compactor parameters (Tables 10 and 11) to the AW 200 compactor was developed using a placebo blend, as it exhibited similar compaction responses as the 5% active preblend formulation. To accomplish this, the AW 50 compactor pressure per cm roll length was determined and translated to an equivalent AW 200 compactor pressure per cm roll length. This normalized the scale-up pressure from the smaller compactor's rolls to the larger compactor's rolls. The AW 50 compactor selected optimized hydraulic roll pressure range was 25–45 bar, (Table 11). The associated range of pressure translated to 4.10–7.40 kN force/cm roll length (Table 12).

The corresponding AW 200 force/cm roll length of 4.10–7.40 kN translated to ~50–85 bar. Therefore, the optimized roller compactor

Table 10 Roller Compactor Operating Conditions and Particle Size Distributions for 5% Active Granulation Trials

	Trial 1	Trial 2	Trial 3
Roll pressure (bar)	21	23	20
Roll speed (rpm)	20	20	20
Screw speed (rpm)	21	21	21
Vacuum pressure, (in./Hg)	0.40	0.40	0.40
Ribbon gauge (mm)	1.42	1.44	1.35
	(% retained)[a]		
Screen size	Trial 1	Trial 2	Trial 3
20	10.6	9.2	8.0
40	29.8	35.8	26.6
60	12.0	12.8	12.2
80	7.8	9.0	8.6
100	6.4	5.4	6.6
200	14.0	11.8	15.4
Pan	20.0	6.7	9.3

[a]% retained on screen (test performed on shaker sifter, 50 g sample).

Table 11 Expanded AW 50 Operating Conditions for 5% Active Granulation with Particle Size Distribution Data[a]

Roll pressure	RP = 25	RP = 35	RP = 45	RP = 45
Roll speed	RS = 20	RS = 14	RS = 14	RS = 20
Screw speed	SS = 20	SS = 16	SS = 20	SS = 20
	(% retained)[b]			
Screen size	Trial 1	Trial 2	Trial 3	Trial 4
20	1.3	1.5	1.3	3.1
30	25.7	26.5	28.1	30.4
40	13.5	14.9	15.4	15.9
60	12.2	12.9	13.6	12.8
140	19.1	17.6	18.4	16.4
270	26.7	24.9	22.1	20.2
Pan	1.5	1.7	1.1	1.2

[a]Units: RP, bar, RS and SS, rpm.
[b]% retained on screen (test performed on shaker type sifter, 50 gram sample).

Table 12 AW 50 and 200 Compactor Conversion Pressing Power

WP50 pressure (bar)	Total pressure		Pressure/cm roll length kNt	
	(kN)	(ton)	(kN)	(ton)
25	30.7	3.07	4.10	0.41
30	36.9	3.69	4.92	0.49
35	43.0	4.30	5.74	0.57
40	49.2	4.92	6.56	0.66
45	55.4	5.54	7.40	0.74
WP200 pressure (bar)				
40	26.08	2.61	3.48	0.35
50	32.57	3.26	4.34	0.43
60	39.12	3.91	5.22	0.52
70	45.63	4.56	6.08	0.61
80	52.11	5.21	6.95	0.70
90	58.66	5.87	7.82	0.78

Source: Data courtesy of Alexanderwerk Inc., Horsham, Pennsylvania, U.S.A.

processing parameters i.e., roll and feed screw speeds, were defined within the AW 200 roll pressure range of 50–85 bar while processing the placebo blend.

The compaction processing parameters selected for roll and screw feed speeds were based on the motor drive working load capacities and equipment operating experience. The precrusher and final sizing granulators were fitted with 4 and 1 mm, respectively, and were operated at determined speeds that effectively voided compacted material from each granulator (in series) and also within motor drive working load capacities. Based on the above criteria, the roll speed range 17–19 rpm, and feed screw speed range 80–90 rpm were evaluated in a 2^4 matrix. Sixteen compactor-processing trials determined: machine operating conditions, compact physical parameters and retained sieve fractions. Six processing conditions were selected for repeat evaluations during the second day to confirm initial results. Ultimately, one processing condition was selected to complete the balance of the placebo scale-up trial: roll speed 17 rpm, feed screw speed 80 rpm, and roll pressure 81 bar. The resultant placebo sieve cut fractions at specific prescribed AW 200 compactor operating conditions compared favorably to the AW 50 compactor sieve cut fraction range of the 5% active granulations (Table 13).

In summary, the AW 50 to AW 200 scale-up placebo procedures described above successfully translated, as expected, into an active 5% granulation using the AW 200 and the parameters defined.

Table 13 AW 200 Placebo and AW 50 Active 5% Comparative Granulometries

Screen size	AW 200 Placebo granulometry percent retained	AW 50, 5% active granulometry percent retained (range)
20	8.3	2–12
30	26.6	11–25
40	15.9	9–16
60	13.5	11–17
100	9.4	8–21
270	17.0	17–21
Pan	9.4	10–33

Roller Compaction Scale-Up Using Near Infrared (NIR) Technology

The following two sections illustrate the use of near infrared (NIR) technology to better understand roller compaction scale-up. This first section addresses the use of NIR to evaluate roller compaction pre- and postblends. Even given the stated advantages of roller compaction, pharmaceutical excipient aids still need to be added to a blend prior to roller compaction. These excipients aid in two important ways, internally and externally, to the formulation processing. Internally, the excipients are needed to aid formulation characteristics such as bonding, disintegration, and dissolution. Externally, specific excipients are needed to make the powder machine perform well during the roller compaction process, e.g., lubricants to aid in powder slippage and minimize potential roll sticking, and powder flow aids to assist powder flow into the compactor hopper during processing. The nature of the roller compaction preblend is important for a number of reasons as stated, including the active pharmaceutical ingredient uniformity. The use of NIR allows the monitoring of roller compaction preblends in a blender to determine when a blend is uniform and ready for the next processing step. Typically, the last pharmaceutical ingredient added to a blender prior to processing the blend is a lubricant.

Usually, the pharmaceutical lubricant of choice is magnesium stearate (2). Magnesium stearate's special NIR spectral features make it easy to monitor in a blending unit operation. The minimization of the magnesium stearate spectral variance correlates directly to the distribution of the magnesium stearate's uniformity in the blend. Figure 1 is a plot of the spectral moving block variance versus the number of blender rotations, as developed by Dr. Tim Stevens, and shows the minimization of the magnesium stearate spectral variance from one rotation to the next. It describes the determination for NIR monitoring of a preblend containing 0.25% magnesium stearate,

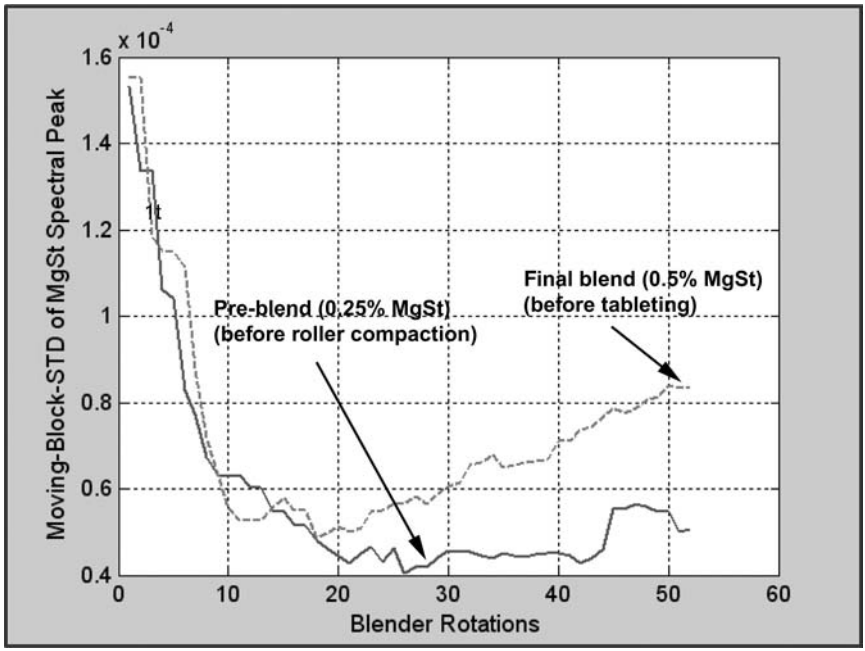

Figure 1 NIR blend monitoring of magnesium stearate in a roller compaction preblend and final blend.

indicating that between 20 and 43 rotations (solid line), the magnesium stearate reaches a minimum standard deviation (minimum spectral variability) and that one can conclude that the lubricant is uniformly blended.

Typically, after processing the roller compaction preblend into a compact, which is then sized into granules, there is a final blend step. This operation consists of adding some additional excipients, plus a lubricant such as magnesium stearate as a processing aid for either tablet compression or encapsulation unit operations. Figure 1 describes the NIR monitoring (dotted line) of the final blend that contains an additional 0.50% magnesium stearate. In this case, it appears that minimization of the magnesium stearate spectral variance is between 20 and 22 blend rotations, suggesting blend lubricant uniformity in this region. Also observed is that subsequent rotations lead to more magnesium stearate spectral variance. This may suggest possible increased non-uniformity of the lubricant in the blend. Although, another possible explanation is that the lubricant blend time may have made the powder blend highly fluid, approaching water-like movement. One can imagine powder moving like water in a blender and its chaotic moving dynamic state. The spectrometer sees varying quantities of material per rotation (different packing densities) and thereby sees differing spectral

fingerprints from rotation to rotation. Work has started to understand this phenomenon more fully.

In summary, it appears that roller compaction pre- and postblends can be NIR monitored during scale-up, independent of batch size and blender type. Using real time NIR monitoring would advance blender unit operations knowledge and provide continuous information and assurance about specific unit operations such as roller compaction, a key FDA Process Analytical Technology goal.

This second section illustrates the continuous monitoring of roller compaction to control key compact parameters such as content uniformity, moisture content, compact density, tensile strength, and postmilling particle size distribution. Understanding and controlling these attributes are desired during roller compaction to ensure consistency in the final product. The FDA's recent initiative, process analytical technologies (PAT), also encourages the use of technology for "continuous real time quality assurance" (9,10). The initiative advocates building quality into the product by "adoption of at-/on-/in-line measurement of performance attributes and real-time or rapid feedback controls (10)." NIR makes it possible to non-destructively and simultaneously analyze multiple constituents present in any matrix. This eliminates the lag time associated with the waiting period for the lab results at the end of each unit operation. NIR also provides the "continuous real time quality assurance" as suggested by the FDA in the PAT initiative (10).

The use of NIR technology to monitor some of the compact parameters has been reported. Gupta et al. (11) observed a linear relationship between the compact strength and the slope of the best-fit line through the NIR spectrum. They also observed a monotonic relationship between the particle size distribution of the postmilled granules and the spectral slopes. Compacts were prepared on a Fitzpatrick roller compactor, model IR 220 (Fitzpatrick Co., Elmhurst, Illinois, U.S.A.) from 100% microcrystalline cellulose as well as from a model formulation containing 10% w/w tolmetin sodium dihydrate active drug substance. In all cases, the above relationships were found to be valid for samples prepared at different roller compactor roll speed settings (Figs. 2 and 3) even when the speeds of the compactor rolls and the vertical feed and horizontal feed screws were changed simultaneously. Roller compacting the 10% tolmetin sodium dihydrate formulation was also monitored in real time using an NIR sensor, the spectral slope was calculated in real time. Compaction run time was four minutes at each speed setting. As evident from Figure 4, the slope of the NIR spectrum was able to track the changes in the compact's strength with changing roller compactor settings. They also observed good agreement between the real-time slope values and the slope values obtained for the spectral data collected off-line on the same compact samples (Fig. 4).

In a later study, the authors found the above relationship between the compact's strength and the slope of the spectral best-fit line to be dependent

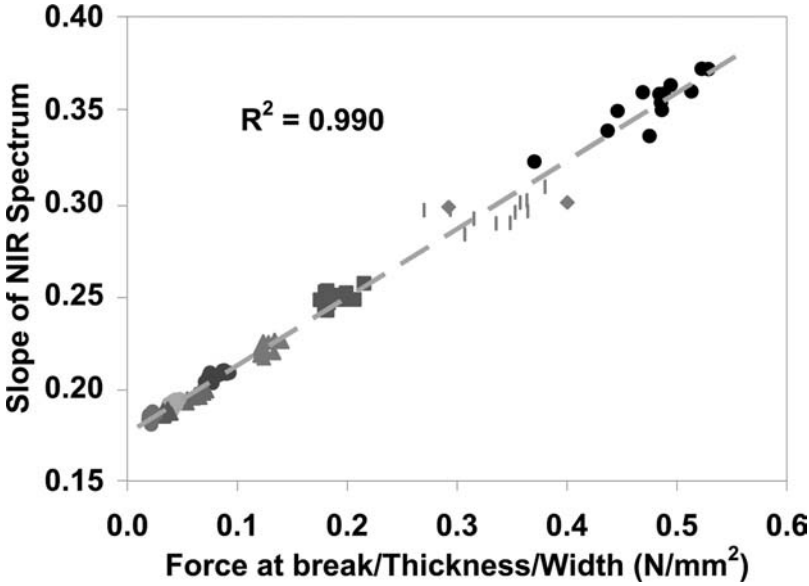

Figure 2 The slope of the best-fit line through the spectrum as a function of normalized force values for the 100% MCC compacts that were prepared at different roll-speeds. The plot shows a linear relationship between the two values.

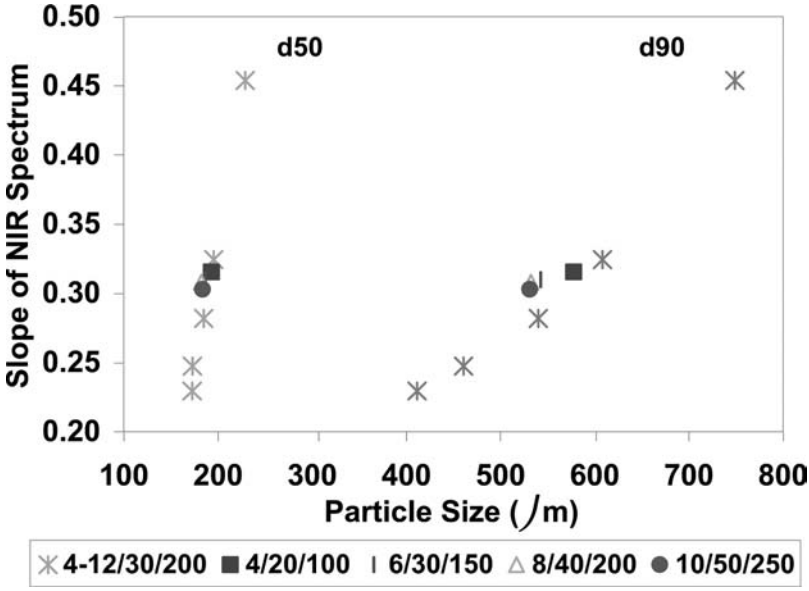

Figure 3 Plot of d90 and d50 values for the 10% tolmetin granules versus the slope of best-fit line showing good agreement between the values from the compacts prepared under two different sets of roller compactor roll/HFS/VFS speed settings.

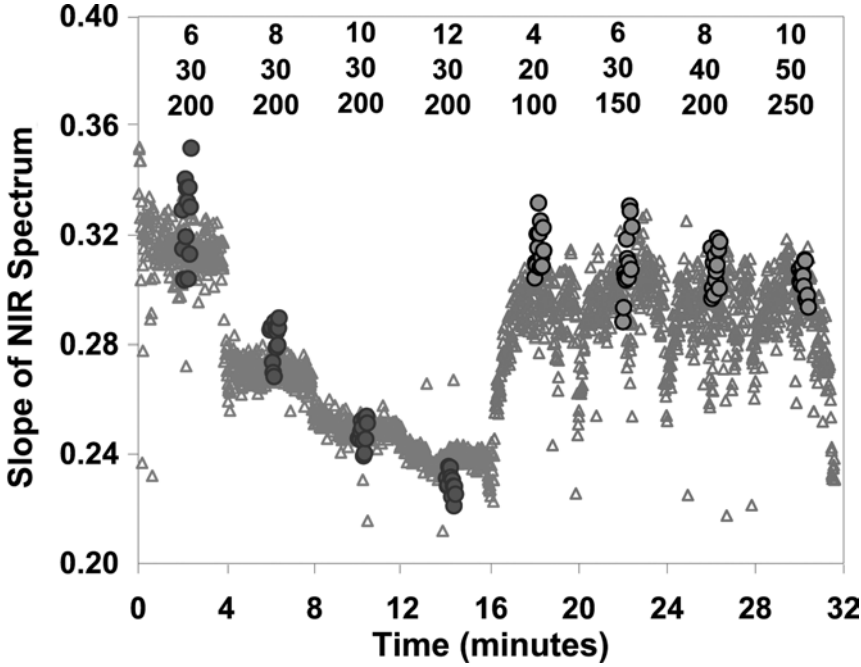

Figure 4 Comparison of the offline slope values (filled circles) with the real-time slope values (open triangles) for the 10% tolmetin compacts prepared at different roller compactor settings. Values on top are the roll, HFS, and VFS speeds, respectively.

on the moisture content of the roller compacted powder (Fig. 5). They also found a significant influence by moisture on the physical and mechanical properties, such as density, strength, etc., of the compacts as well as on the postmilled particle size distribution. The postmilled particle size distribution was found, however, to be dependent on the tensile strength of the compacts (11).

NIR Monitoring of Roller Compaction Scale-Up

Figure 5 shows the results of the authors' study on the ability of NIR to monitor the scale-up from the laboratory Carver Press to the Fitzpatrick roller compactor. Because the NIR signal is influenced by changes in the physical and mechanical properties, multivariate data analysis techniques were used to identify and separate these contributions in the overall NIR signal. A flat-faced rectangular die and punch set, 40×15 mm in size, was fitted on the laboratory Carver Press to prepare tablets similar in shape and size to the roller compacted samples.

Initially, 100% microcrystalline cellulose (MCC) (Avicel PH 200, FMC Corp. Newark, Delaware, U.S.A.) powder was used as the model compound

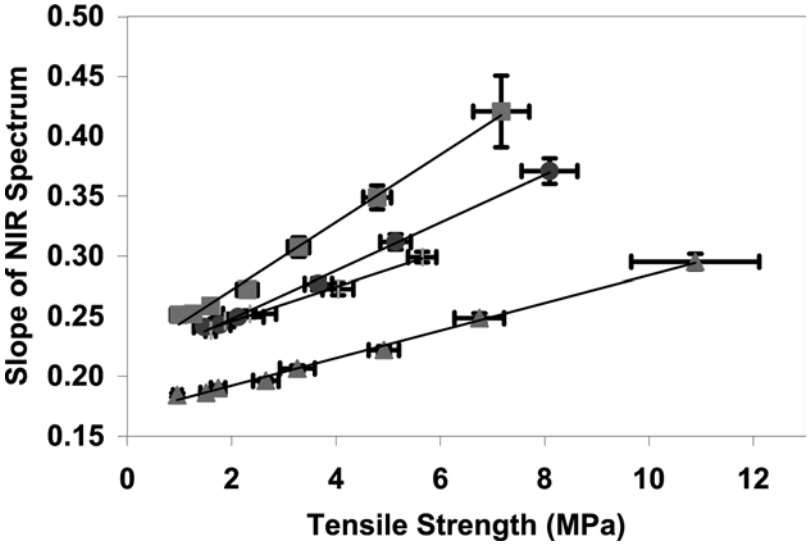

Figure 5 Relationship between the slope of the NIR spectrum and the tensile strength of the corresponding roller compacted sample at different moisture quantities. Triangles, 3.5%; diamonds, 4.6%; circles, 5.7%; and squares, 7.2% LOD samples.

for feasibility studies. Tablets, weighing approximately 2 g each ($n = 6$), were compressed from the MCC powder at compression pressures from 10 to 90 MPa in increments of 10 MPa. Different moisture contents were obtained by equilibrating the MCC powder under relative humidity (RH) conditions between 15% and 75% and compressing under the same RH conditions for equilibrating the powders. The relative humidity range used represents powder moisture content from 2.5% to 8.5% w/w on wet weight basis. Key sample attributes of moisture content, density, tensile strength and Young's modulus were measured for all tablets. Moisture content was determined by loss on drying (LOD) method; density (ρ) from sample weight and volume measurements; and tensile strength and Young's modulus using the three-point beam bending method on a TA.XT2i Texture Analyzer (Texture Technologies Corp., Scarsdale, New York, U.S.A.; Stable Micro Systems, Godalming, Surrey, U.K.). True density (ρ_{true}) of 100% MCC powder was determined using helium pycnometer (AccuPyc 1330, Micromeritics Instrument Corporation, Norcross, Georgia, U.S.A.) following the manufacturer's recommended procedure. Sample densities were converted to relative densities by correcting for the contribution of water using the formula $D = 100{*}\rho/[(100 - \text{LOD})^{*}\rho_{\text{true}} + \text{LOD}]$. NIR spectra were also collected for all tablets.

Moisture content, density, and tensile strength of the sample are known and were found to influence the NIR spectra. Hence, multivariate data analysis

by partial least-squares projections to latent structures (PLS) was used to separate these confounding signals. PLS is a mathematical procedure commonly used for resolving sets of data into latent variables, i.e., principle components (PCs), whose linear combinations approximate the original data to any desired degree of accuracy. The latent variables areconstructed in such a way so as to account for the maximum amount of covariance between the dependent and the independent variables. Successive components are calculated orthogonally to the preceding components with each component accounting for the maximum possible amount of residual variance in the data set, followed by cross-validation to prevent over-fitting of the data.

Different spectral preprocessing and transformations available in SIMCA P + (version 10.0, Umetrics, Sweden) were evaluated and the best approach for data handling and manipulation was determined. Data collected on the surrogate tablets were divided into a training set to generate the PLS models, and prediction set to test the PLS models. MCC powder, equilibrated at different RH, was also roller compacted at different roll speeds on a Fitzpatrick IR220 roller compactor fitted with smooth rolls. Powder feed rate and roll pressure were kept constant for all experiments. The key sample attributes measured on the surrogate tablets were also measured for the samples prepared by roller compaction.

Good agreement was observed between the NIR-PLS predicted values and the values determined using the reference methods for all key attributes for the surrogate tablets, as well as for the samples prepared by roller compaction. A number of PLS models, generated using different data preprocessing and transformations, gave satisfactory results. However, the best results were obtained when the spectral data were transformed using the multiplicative signal correction (MSC) followed by mean centering and three principal components (PC) were used (Fig. 6). Because PCs represent the separated contribution of different sample attributes to the overall NIR signal, they were related to the sample attributes used in this study.

The first PC quantified the moisture content as evident from the strong contribution around 1930 nm region, which represents the combination band of the –OH stretching and –OH bending vibrations. The second PC quantified the baseline shift due to changing sample density as a result of changing compression pressures. The third PC quantified the changes in MCC structure as evident from its resemblance with NIR spectrum collected on the 100% MCC powder sample. The root mean-square errors of prediction for different sample properties are summarized in Table 14.

The study was then extended to monitor the scale-up of a pharmaceutical blend containing an active pharmaceutical ingredient. A binary mixture of acetaminophen (APAP) with microcrystalline cellulose was selected as the model formulation. The ability of NIR spectroscopy to monitor real-time content uniformity in addition to the aforementioned compact attributes, during roller compaction was also tested.

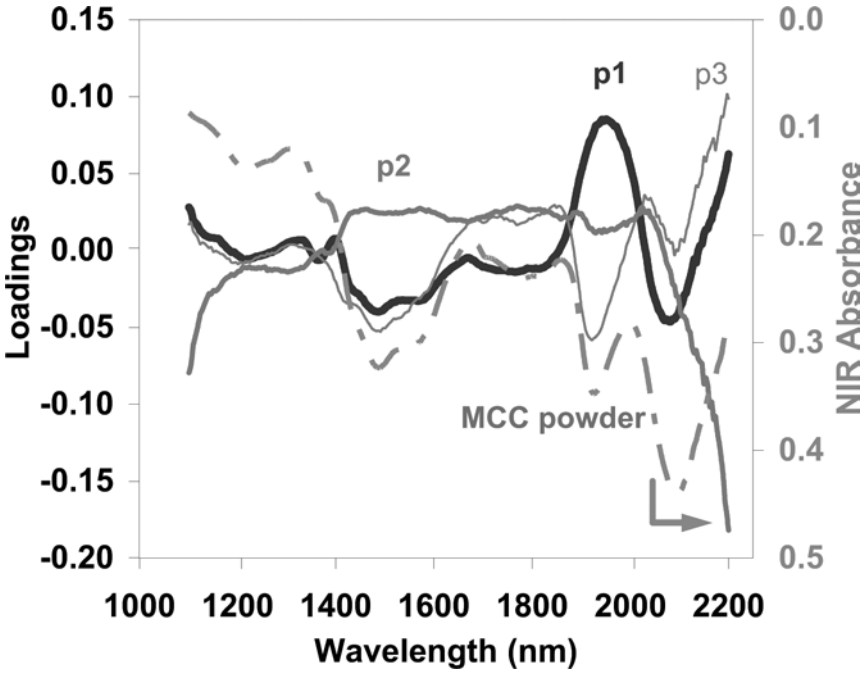

Figure 6 The first three loading vectors of the NIR PLS model generated on the surrogate MCC tablets. *Key*: p1, very thick line; p2, thick line; p3, thin line; and NIR spectrum of 100% MCC powder, dashed line.

NIR calibration curves were prepared by measuring the key compact attributes on rectangular surrogate tablets, prepared on the laboratory Carver press. The preparation of the calibration curve requires samples with attributes spanning the range of values likely to be encountered during roller compaction. Hence, drug content (for content uniformity), relative humidity

Table 14 Root Mean Squares Errors for the NIR-PLS Predicted Values of Different Sample Attributes for the MCC Surrogate Tablets and Roller Compacted Samples

Data set	LOD (% w/w)	*D*	TS (MPa)	*E* (GPa)
Training set (tablets)	0.38	0.043	0.99	0.13
Prediction set 1 (tablets)	0.38	0.033	0.86	0.13
Prediction set 2 (compacts)	0.72	0.074	1.49	0.36

Abbreviations: LOD, loss on drying; *D*, relative density; TS, tensile strength; *E*, Young's modulus.

(for moisture content) and compression pressure (for density, tensile strength, and Young's modulus) were selected as the three variables for establishing the conditions required for preparing the surrogate tablets. The actual conditions of these three variables were selected using two different experimental designs, namely, the Latin square design and the extreme vertices analysis. Experiments using the Latin square design can have 3, 4, or 5 levels each, of all three variables, resulting in 9, 16, or 25 experiments, respectively, instead of 27, 64, or 125 experiments if all combinations of the three variables were tested. Because the multivariate analysis of data requires more data points for higher accuracy, the Latin square design involving five levels of each of all three variables was selected (Table 15).

The extreme vertices analysis, involving three variables at three levels each, was also evaluated. The extreme vertices experimental design reduced the number of experiments to 15 versus 27 if all combinations of the three variables were tested. The 15 experiments represent the eight experiments having the highest or the lowest level of each variable and seven experiments with at least two variables at the middle level. Tablets, weighing approximately 2 g each ($n = 6$), were compressed from different powder blends at compression pressures according to the experimental designs outlined above. When equilibrating and compressing the above powder blends at different RH conditions (15, 32, 43, 60, and 68%), different moisture contents were obtained. No internal or external lubricant was used during the preparation of tablets. All tablet surfaces were found to be free from visible defects upon ejection.

The 10% w/w APAP powder blend was roller compacted. Different moisture contents were achieved by equilibrating and roller compacting the above powder blend under 24, 45, and 65% RH conditions, representing 3.3, 5.0, and 6.3% w/w moisture content, respectively. Compacts were prepared at 5.0, 6.0, and 7.2 rpm roll speeds with the powder feed rate and roll pressure kept constant. Compaction run time was four minutes at each roll speed. Samples were also collected for off-line measurements of

Table 15 APAP Content, RH and Pressure Combinations Selected Using the Latin Squares Experimental Design for Preparing Surrogate Tablets

Pressure (MPa)		Relative humidity (%)				
		15	30	45	60	75
APAP content (% w/w)	6	10	30	50	70	90
	8	50	70	90	10	30
	10	90	10	30	50	70
	12	30	50	70	90	10
	14	70	90	10	30	50

the key sample attributes. Real-time monitoring of roller compaction was also performed.

Data collected on the surrogate tablets were divided into the training and prediction sets. Three different PLS models with different training sets were evaluated. Data collected on surrogate tablets prepared with the Latin square experimental design, extreme vertices experimental design, and the combined data from the two experimental designs, respectively, were used as the data for the three training sets. Tablet data from the other experimental design for the first two PLS models (prediction set 1) and the data collected during real-time monitoring of roller compaction (prediction set 2) were used to evaluate the above PLS models. In all cases, data were subjected to MSC followed by mean centering before the use of PLS analysis.

PLS models generated using different training set data gave satisfactory results in all three cases. For all five sample attributes, good agreement was observed between the NIR predicted and measured values. However, best results were obtained with the PLS model generated on the data collected using the Latin square experimental design when four PCs were used (Fig. 7). In all models, the first PC quantified the moisture content of the samples, and the second and third PCs together quantified the APAP

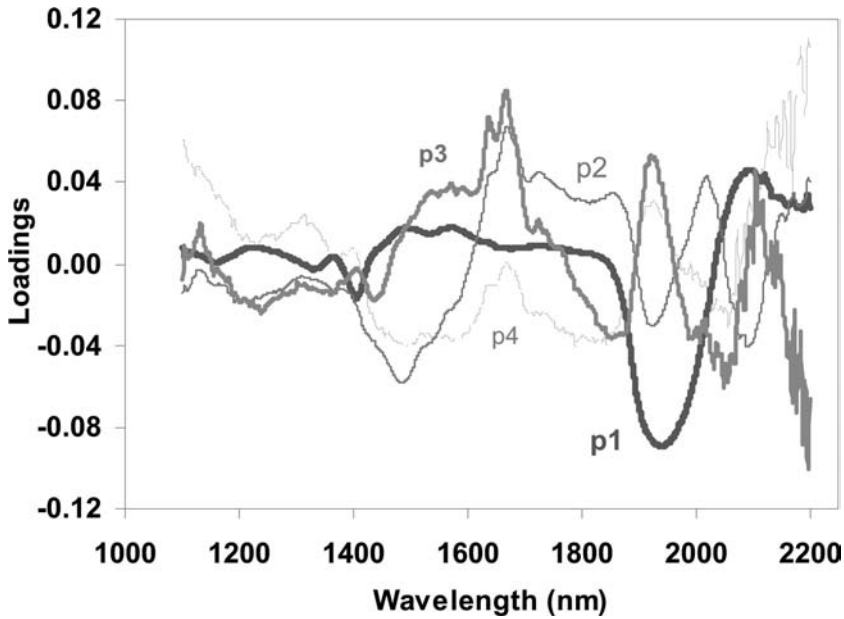

Figure 7 The first four loading vectors of the NIR PLS model (MSC and mean centering) generated on the NIR data collected on the 10% APAP surrogate tablets prepared according to the Latin square experimental design.

concentration, relative density, tensile strength and Young's modulus. The fourth PC accounted for the day-to-day variation in data collection and to improve the predictability of the PLS models.

The PLS model generated on samples prepared according to the Latin squares experimental design was used to predict the key compact attributes from the real-time spectral data collected for roller compacted samples (Fig. 8). Good agreement was observed between the NIR-predicted values and the values measured off-line using the reference methods (Table 16).

Very little scatter was observed in the PLS predicted values for sample LOD (Table 16) and APAP concentration (Fig. 9).

However, large scatter was observed in the case of the NIR-PLS predicted values for tensile strength, Young's modulus, and relative density (Fig. 10). Powder by-pass along the side seals is a common problem encountered during roller compaction. Continuous but small amounts of powder by-pass occurred during all roller compaction experiments reported above, resulting in generation of dust clouds in the region below the roller compactor. Because the NIR sensor was also positioned in this region, the presence of the dust cloud between the sensor and the ribbon and the powder by-pass might have affected the NIR signal. This may be the reason for the large scattering observed in the NIR-PLS predicted values of relative density,

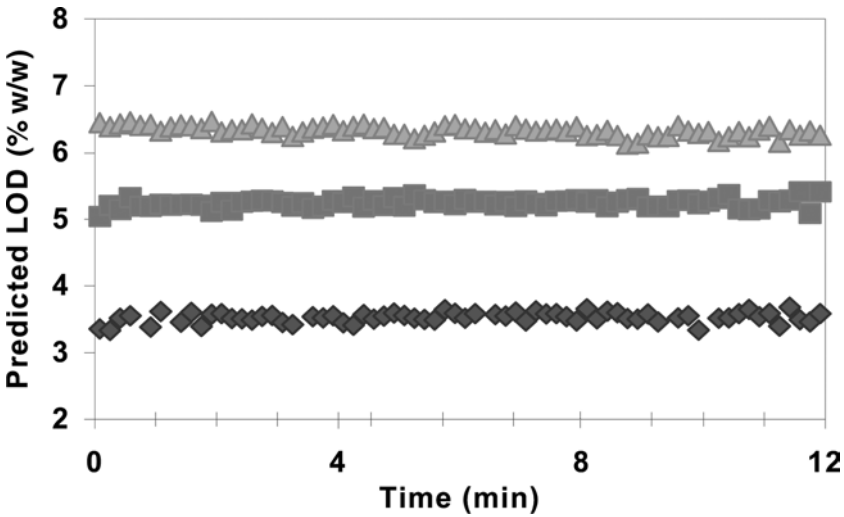

Figure 8 PLS predicted values of LOD from the NIR data collected during real-time monitoring of roller compaction at different RH. *Key*: Diamonds, 24% RH; squares, 45% RH; triangles, 65% RH. Four minutes each at 7.2, 6.0, and 5.0 rpm roll speeds, respectively.

Table 16 Comparison of the Measured and NIR Predicted Values for Different Sample Properties for Compacts Prepared at Different Roll Speeds and RH Conditions

		Measured at roll speed			NIR predicted at roll speed		
Property	RH	7.2	6.0	5.0	7.2	6.0	5.0
APAP concentration (% w/w)	24	10.1 (0.6)	10.05 (0.6)	9.8 (0.6)	10.2 (0.8)	9.7 (1.0)	9.1 (0.9)
	45	10.2 (0.5)	9.9 (0.6)	9.9 (0.6)	10.1 (0.7)	10.0 (0.7)	9.8 (0.8)
	65	9.5 (0.4)	9.3 (0.4)	9.3 (0.5)	9.5 (0.7)	8.9 (0.6)	8.8 (0.6)
Relative density	24	0.68 (0.01)	0.70 (0.01)	0.76 (0.01)	0.69 (0.04)	0.72 (0.08)	0.74 (0.10)
	45	0.72 (0.02)	0.78 (0.02)	0.79 (0.02)	0.72 (0.05)	0.77 (0.06)	0.87 (0.09)
	65	0.73 (0.02)	0.77 (0.02)	0.81 (0.03)	0.75 (0.04)	0.84 (0.07)	0.93 (0.08)
Loss on drying (% w/w)	24	3.3[a] (0.1)	3.3[a] (0.1)	3.3[a] (0.1)	3.5 (0.1)	3.5 (0.1)	3.6 (0.1)
	45	5.0[a] (0.1)	5.0[a] (0.1)	5.0[a] (0.1)	5.2 (0.1)	5.2 (0.1)	5.2 (0.1)
	65	6.3[a] (0.03)	6.3[a] (0.03)	6.3[a] (0.03)	6.4 (0.1)	6.4 (0.1)	6.3 (0.1)
Tensile strength (MPa)	24	2.9 (0.3)	3.2 (0.4)	4.9 (0.3)	3.6 (0.7)	4.4 (1.5)	5.1 (1.8)
	45	3.3 (0.2)	5.3 (0.3)	6.9 (0.5)	2.9 (0.9)	4.0 (1.3)	6.1 (1.7)
	65	2.5 (0.2)	3.9 (0.2)	5.5 (0.6)	3.0 (0.7)	5.2 (1.4)	7.4 (1.8)
Young's modulus (GPa)	24	0.56 (0.07)	0.59 (0.08)	0.87 (0.08)	0.61 (0.12)	0.72 (0.24)	0.81 (0.30)
	45	0.57 (0.05)	0.91 (0.06)	1.27 (0.07)	0.54 (0.14)	0.70 (0.20)	1.02 (0.28)
	65	0.44 (0.04)	0.64 (0.03)	0.75 (0.14)	0.56 (0.11)	0.90 (0.22)	1.20 (0.28)

[a]LOD values determined on the powder blend used for roller compaction.

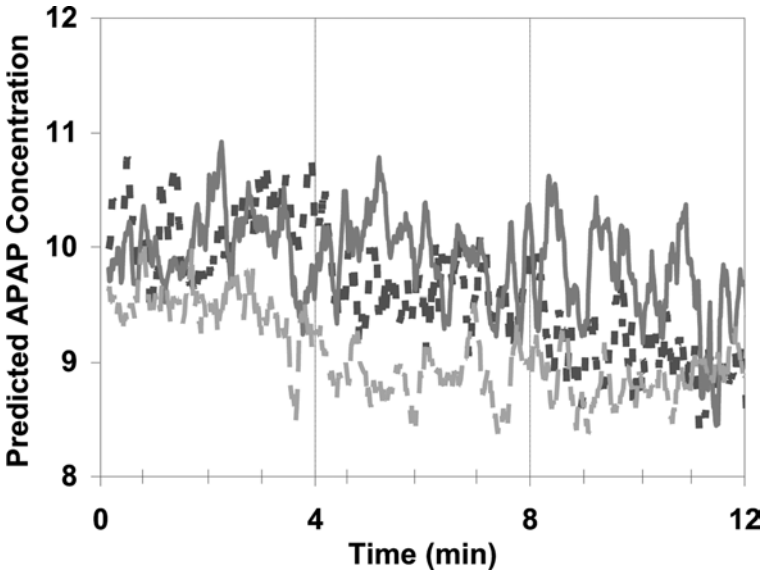

Figure 9 PLS predicted values of APAP concentration from the NIR data collected during real-time monitoring of roller compaction at different RH. *Key*: - - - -; 24% RH, ——; 45% RH, — —; 65% RH. Four minutes each at 7.2, 6.0, and 5.0 rpm roll speeds, respectively.

tensile strength, and Young's modulus. No such dust cloud was present during the data collection of the surrogated tablets.

CONCLUSION

The studies discussed herein demonstrated that NIR diffuse reflectance spectroscopy may be used as a rapid, non-destructive and non-invasive method for real-time monitoring and control of key compact attributes during roller compaction. The NIR predicted values for all compact attributes agreed well with the results obtained using the reference methods. The small difference between the measured and the NIR predicted values of some of the attributes highlights the importance of controlling the environmental conditions during data collection of the training set samples. The authors recommend collecting training set data in an environment that represents the conditions around the sensor during real-time monitoring of the unit operation. The advantage of NIR real-time roller compaction monitoring is that it provides instantaneous feedback and determination of environmental or process change effects, such as RH, roll speed, etc. Also, it predicts the influence of such changes on key compact attributes. The above technique

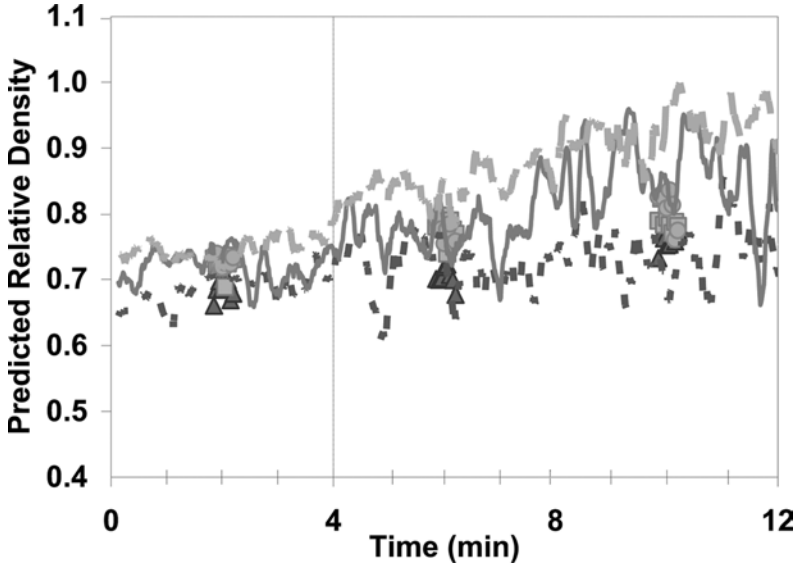

Figure 10 PLS predicted relative densities from the NIR data collected during real-time monitoring of roller compaction at different RH, - - - -; 24% RH. *Key*: ——; 45% RH, — —; 65% RH. Four minutes each at 7.2, 6.0, and 5.0 rpm roll speeds, respectively. The measured values at the three RH are plotted as triangles, squares, and circles, respectively.

has potential use in real-time monitoring of similar attributes of tablets produced by high-speed tablet machines.

ACKNOWLEDGMENTS

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10

Batch Size Increase in Fluid-Bed Granulation

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INTRODUCTION

The size enlargement of primary particles has been carried out in the pharmaceutical industry in a variety of ways. One of the most common unit operations used in the pharmaceutical industry is fluid-bed processing. The batch size increase using fluid-bed granulation requires a good understanding of equipment functionality, the theoretical aspect of fluidization, excipient interactions, and most of all, identifying the critical variables that affect the process of agglomeration.

This chapter will provide an essential understanding of the fluidization theory, a system description of the fluid-bed processor, and will discuss the critical variables associated with equipment, product and process. Upon gaining this basic understanding, one can design scale-up protocols. These protocols will be able to assure that the probability of successful transition from the R&D batch sizes to the pilot size batches and ultimately to the commercial scale will be high. As in any unit operation that requires batch size increase, fluid-bed process must undergo process qualification to establish the robustness of the process. How critically these process variables are identified at an early stage of the product development and then extrapolated based on the knowledge of the equipment variables and tolerances, and material handling considerations, will provide the trouble-free batch size increase. Fluidized bed granulation is a process by which granules are

produced in a single piece of equipment by spraying a binder solution onto a fluidized powder bed. This process is sometimes classified as the one-pot system. The fluid-bed granulation process has received considerable attention within the pharmaceutical industry; however, other process industries, such as food, agro-chemical, dyestuffs, and other chemical industries, have adopted the fluid-bed granulation process to address particle agglomeration, dust containment, and material handling. The fluidization technique, as it is known today, began in 1942, with the work of the Standard Oil Company (now known as Exxon, in the United States) and M.W. Kellogg Company, in an effort to produce the first catalytic cracking plant on a commercial scale (1).

Fluid-bed processing of pharmaceuticals was first reported by Wurster, when he used the air-suspension technique to coat tablets (2,3). In 1960, he reported on granulating and drying a pharmaceutical granulation, suitable for the preparation of compressed tablets, using the air-suspension technique. In 1964, Scott et al. (4) and Rankell et al. (5) reported on the theory and design considerations of the process, using a fundamental engineering approach and employing mass and thermal energy balances. They expanded this application to the 30-kg capacity pilot plant model designed for both batch and continuous operation. Process variables, such as airflow rate, process air temperature, and liquid flow rate, were studied. Contini and Atasoy (6) later reported the processing details and advantages of the fluid-bed process in one continuous step. Wolf (7) discussed the essential construction features of the various fluid-bed components, and Liske and Mobus (8) compared the fluidized bed and traditional granulation process. The overall results indicated that the material processed by the fluid-bed granulator was finer, more free-flowing, and had homogeneous granules which, after compression, produced stronger and faster disintegration of tablets than the materials processed by conventional wet granulation. Reviews by Sherrington and Oliver (9), Pietch (10), and a series published on the topic of "Fluidization in the Pharmaceutical Industry" (11–17) provide an in-depth background on the fundamental aspects of the fluidized bed and other granulation technologies. The fluidized bed was used only for efficiently drying the pharmaceutical granulation in the early days, but now is employed routinely for drying, agglomeration, pelletization, and production of modified-release dosage forms using air-suspension coating. Because of this, these units are normally classified as multi-processor fluid-bed units.

Fluidization Theory

Typical fluid-bed processor elements can be seen in Figure 1. The fluidizing gas enters the bed at the bottom through an air distributor. The gas passes up through the bed of solids, causing it to fluidize. This gas/solid mixture behaves much like liquid of similar bulk density. Above the fluidized bed, a freeboard section (expansion chamber) is provided to slow down the

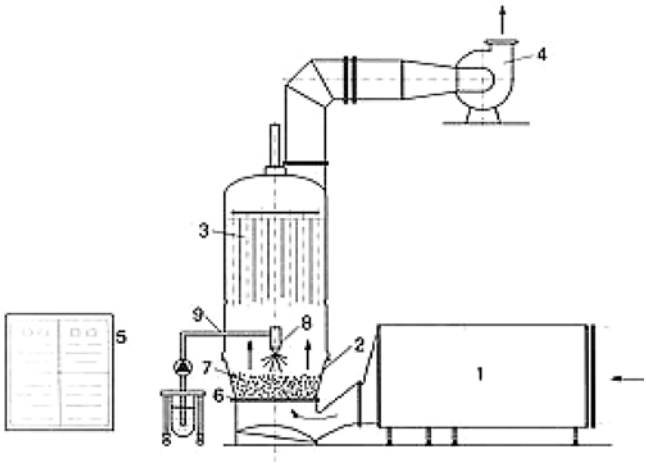

Figure 1 Typical fluid-bed processor.

particle velocity thrown up by bursting bubbles at the bed surface. In addition, the filter bags or cartridges are provided to capture any fines elutriated with the exit gas from the process vessel.

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate great enough to set them in motion, this velocity, according to Kulling and Simon (18), is higher than the incipient fluidizing velocity, but lower than the entrainment velocity. When the rate of gas flow increases, the pressure drop across the bed also increases until, at a certain rate of flow, the frictional drag on the particles equals the effective weight of the bed. These conditions, and the velocity of gas corresponding to it, are termed *incipient fluidization* and *incipient velocity*, respectively. The relationship between the air velocity and the pressure drop is shown in Figure 2.

At low gas velocities, the bed of particles is practically a packed bed, and the pressure drop is proportional to the superficial velocity. As the gas velocity is increased, a point is reached at which the bed behavior changes from fixed particles to suspended particles. The superficial velocity required to first suspend the bed particles is known as *minimum fluidization velocity* (umf). The minimum fluidization velocity sets the lower limit of possible operating velocities and the approximate pressure drop can be used to approximate pumping energy requirements. For agglomeration process in the fluid-bed processor, air velocity required is normally five to six times the minimum fluidization velocity.

At the incipient point of fluidization, the pressure drop of the bed will be very close to the weight of the particles divided by the cross-sectional area of the bed (W/A). For the normal gas fluidized bed, the density of the gas is

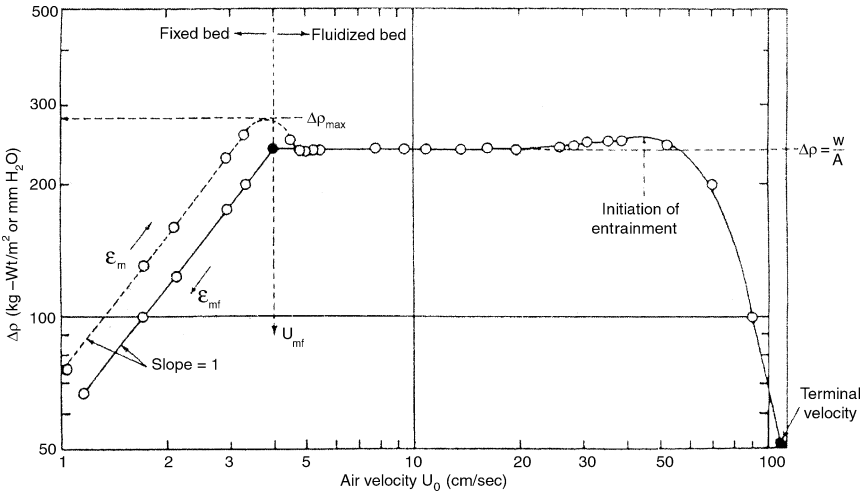

Figure 2 Typical pressure drop curve as a function of gas velocity. *Source*: Adapted from Ref. 19.

much less than the density of the solids and the balance of forces can be shown as a

$$\Delta p \text{ mf} = \text{W/A}$$

where

$$W = (1 - \varepsilon\text{mf})\rho\text{p}.g/g\text{c}$$

where Δp is the pressure drop, εmf the minimum fluidization void fraction, A the cross-sectional area, W the weight of the particles, ρp the density of particles, and g/gc is the ratio of gravitational acceleration and gravitational conversion factor.

As the velocity of the gas is increased further, the bed continues to expand and its height increases with only a slight increase in the pressure drop. As the velocity of the gas is further increased, the bed continues to expand and its height increases, whereas the concentration of particles per unit volume of the bed decreases. At a certain velocity of the fluidizing medium, known as entrainment velocity, particles are carried over by the gas. This phenomenon is called entrainment. When the volumetric concentration of solid particles is uniform throughout the bed at all times, the fluidization is termed as the *particular*. When the concentration of solids is not uniform throughout the bed, and if the concentration keeps fluctuating with time, the fluidization is called aggregative *fluidization.* A *slugging bed* is a fluid-bed in which the gas bubbles occupy entire cross sections of the product container and divide the bed into layers.

A *boiling bed* is a fluid-bed in which the gas bubbles are approximately the same size as the solid particles.

A *channeling bed is* a fluid-bed in which the gas forms channels in the bed through which most of the air passes.

A *spouting bed* is a fluid-bed in which the gas forms a single opening through which some particles flow and fall on the outside. Figure 3 shows various types of fluid-beds (20).

The mechanisms by which air affects fluidization have been discussed by various researchers (21–26). When the fluidizing velocity is greater than the incipient velocity, bubbles of air rise through the bed, causing mixing of particles. Mixing does not generally occur when the bed is fluidized at very low or zero *excess* gas velocities, because insufficient bubbles are formed to cause bulk displacement of particles. It is the gas passing through the bed in the form of bubbles that determines the degree of mixing. The extent of mixing appears to vary with the particle size. Mixing of particles having

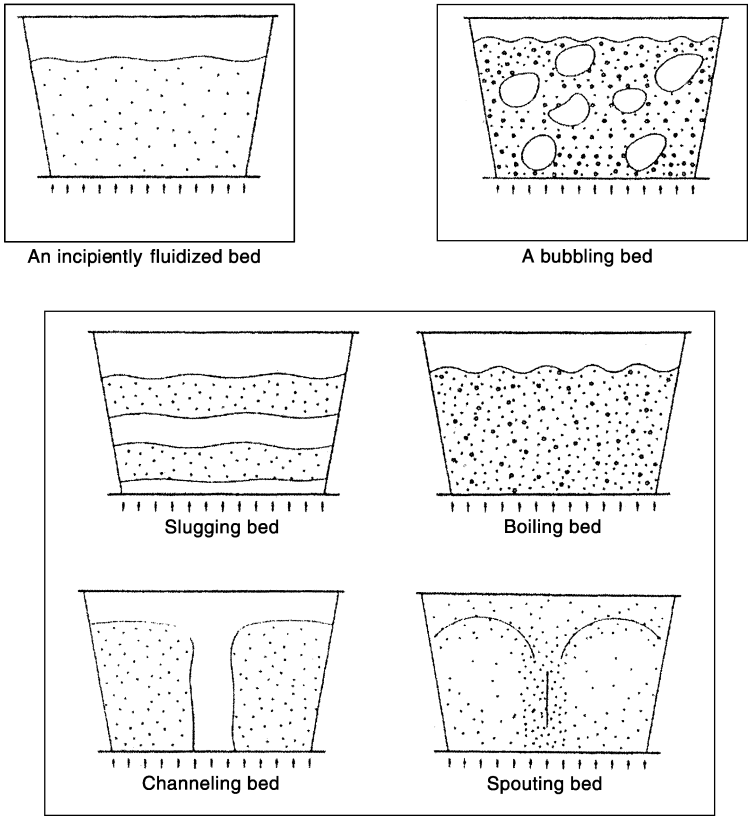

Figure 3 Various types of fluid-beds. *Source*: From Ref. 20.

a mean particle size of less than approximately 150 μm decreases as the mean size approaches zero. Different types of beds, described above, are formed, depending upon the movement of bubbles through the bed. Bubbles play an extremely important role in the motion of particles in the fluidized bed. Solids are carried in the wakes behind rising bubbles. A number of correlations exist for estimating the bubble size in a fluidized bed (27). In general, bubble sizes are fairly small (2–5 cm) for powders that can easily fluidized, while sandy powders also fluidize easily but do not show any particulate expansion, and bubbles grow with bed height to large size and can easily form slugs in narrow diameter beds. The pattern of movement of the gas phase in and out of bubbles depends upon several factors, including minimum fluidization velocity and particle size. These movements affect heat transfer between air bubbles and particles. The air distributor at the bottom of the container has a controlling influence on the uniform distribution of gas, minimization of dead areas and maximization of particle movement. The most common reason for mixing problems, such as segregation in the fluid-bed, is the particle density differences. The extent of segregation can be controlled in part by maintaining high fluidizing velocities and high bowl-height-to-bowl-diameter ratio. There are standard air velocities for various processes that can be used as guidelines. The standard velocities are based upon the cross-sectional area at the bottom of the product container.

This is calculated by using the following formula for calculating the air velocity:

$$\text{Velocity (m/sec)} = \text{Air flow [cubic meter per hour (CMH)]} \div \text{Area (m}^2\text{)} \times 3600.$$

where, air flow in cubic meters per hour (CMH) = air flow (CFM) × 1.696.

Standard air velocities are based on the application. Low air velocities such as 0.8–1.4 m/sec are required for drying. The velocities are higher during the early stages of drying because of the wet mass present in the bowl, but will be reduced, when the product loses its moisture. The objective is to have good particle movement but to keep the material out of filters. Particle movement and quick drying are important during the agglomeration process. Air flow velocities are normally 1.0–2.0 m/sec.

An indication of good fluidization is a free downward flow of the granulation at the sight glass of the drying container. However, improper fluidization can also be detected by monitoring the outlet air temperature. Every product has a unique constant rate of drying in which the bed temperature remains relatively constant for a significant length of time. Therefore, if the outlet temperature rises more rapidly than anticipated, it will indicate an improper fluidization and the process may have to be stopped and manual or mechanical intervention may be required to assist the fluidization.

Mass and Energy Balance

A fluidized bed is a granulator as well as a dryer. It therefore has operational limits that are defined by its ability to evaporate solvent being sprayed in. Often, the energy required to heat the granules is small compared to that required to evaporate the solvent. The exit gas and particles from the fluid-bed have the same temperature as the granules in the bed due to the intense mixing action of the bed. Hence, the mass energy balance limitations are quite evident:

1. The exit gas humidity cannot exceed the saturation humidity in the gas at the exit temperature. Once the exit air is saturated, no more liquid can be removed from the fluid-bed.
2. The energy required to evaporate the liquid cannot exceed that available from the incoming gas.

If either of these limits is exceeded, liquid will accumulate in the bed, causing bed collapse. These limits are the two constraints that must always be met.

SYSTEM DESCRIPTION

A *fluid-bed processor* is a system of unit operations involving heating process air and a system to direct it through the material to be processed and have the same air (usually laden with moisture) exit the unit void of the product. Figure 4 shows a typical fluid-bed processor with all the components. These components and their utility for granulation will be reviewed.

At the downstream end of the fluid-bed processor, an exhaust blower or fan is situated to draw the air through the entire unit. This arrangement

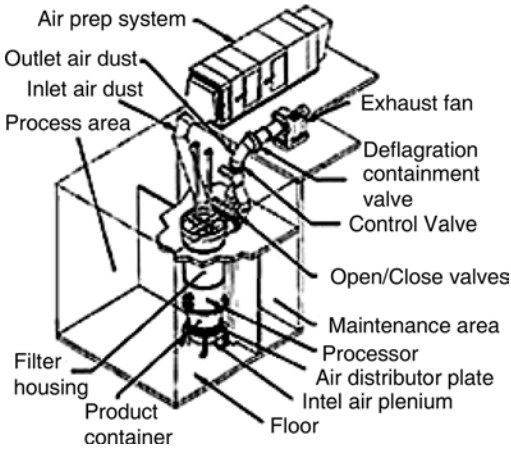

Figure 4 Typical components of a fluid-bed processor.

provides negative pressure in the fluid-bed, which is necessary to facilitate material loading, maintain safe operation, prevent material escape, and carry out the process under good manufacturing practices guidelines, all of which will be discussed later in the chapter.

Air Handling Unit (AHU)

A typical air preparation system includes sections for air filtering, air heating, air cooling, and humidity removal. Generally, outside air is used as the fluidizing medium in a fluid-bed processor. For the air to be used for pharmaceutical products, it must be free of dust and contaminants. This is achieved by placing coarse dust filters (30–85%) in the AHU. Figure 5 shows a typical air handling unit.

After the installation of the filters, distinct heating or cooling sections are installed in the air handler, depending upon the geographical location of the plant. In a extremely cold climate, where cooling coils (needed in summer months for maintaining uniform dew point) can freeze in winter, a preheating section is placed ahead of the cooling coils. A typical range for the air after pretreatment that one should aim at achieving is 15–30°C dry bulb and 3–5°C wet bulb. If the unit is located in a tropical or humid climate, the humidity removal section is employed first. The dehumidification of the air is extremely important, where the outside air moisture varies over a wide range. In summer, when the outside humidity is high, dehumidification of the process air is required to maintain a specific dew point of the incoming process air. Re-humidification may be necessary during the winter months in some regions. A steam injector is used for re-humidifying the dry air. Generally, the lower the process air dew point, the higher the affinity to entrain moisture and the shorter the process time. When granulating extremely fine powders, an inlet air dew point of 15°C is beneficial to reduce static charges and facilitate uniform fluidization. In many processes, when preheating is required, a bypass loop can be used for preconditioning the air. This loop

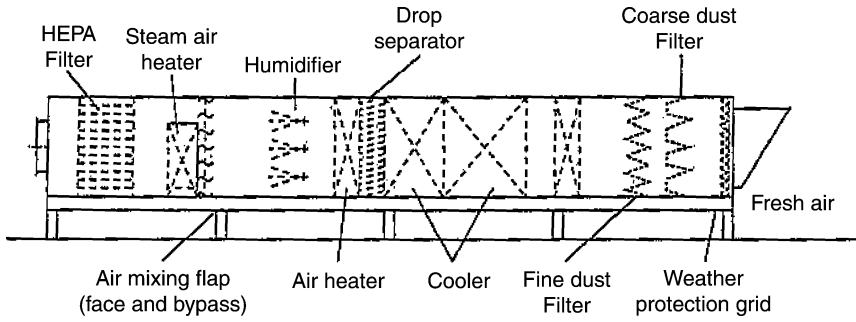

Figure 5 Typical air handling unit for the fluid-bed processor.

allows the required process temperature and humidity to be attained within the system ducts before the product is subjected to fluidization. After the conditioned air leaves the humidification/dehumidification section of the AHU, it is finally heated to the desired process air temperature and then passed through a high efficiency particulate air (HEPA) filter of about 99.90–99.99% capacity. As the process air is treated and filtered, it is transported by the inlet duct. The air is thus brought into the process vessel in the lower plenum.

Product Container and Air Distributor

With the air at the desired humidity and temperature, it is ready to be passed through the bed of solids. Figure 6 shows a typical product container with the air distributor.

The air must be introduced evenly at the bottom of the product container through an inlet air plenum. Proper air flow in the inlet air plenum is critical to ensure that equal air flow velocities occur at every point on the air distributor plate. If the air is not properly distributed before it reaches the bottom of the container, uneven fluidization can occur.

To properly fluidize and mix the material in the container, a correct choice of the container and air distributor must be made. The container volume should be chosen such that the bowl is filled to at least 35–40% of its total volume and no more than 90% of its total volume. Correct choice of the air distributor is important. These distributors are made of stainless steel and are available with a 2–30% open area. Typically, the distributor should be chosen so that the pressure drop across the product bed and air

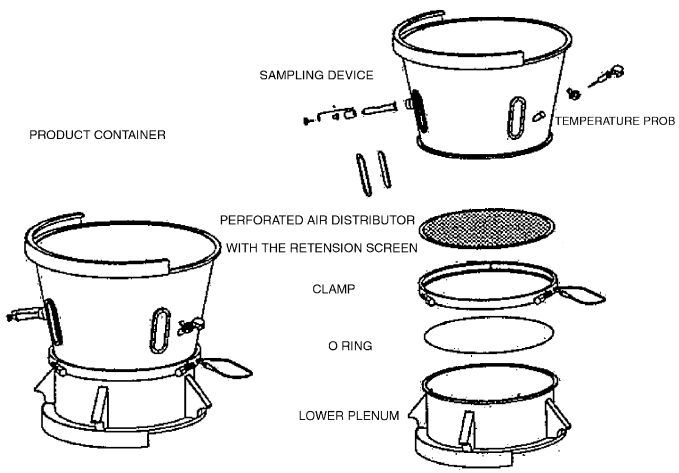

Figure 6 Typical product container with air distributor.

Figure 7 Non-sifting gill air distributor. *Source*: Courtesy of Niro Pharma Systems.

distributor is 200–300 mm of water column. A fine screen of 60–325 mesh normally covers the air distributor and retains the product in the container. This type of sandwiched construction has been used for the last 30 years in the fluid-bed processors. The classic air distributor with the fine product retaining screen is shown in Figure 6.

Keeping the screen and air distributors clean has been challenging. Partially to address the cleaning problems and partially to provide efficient processing, a new overlap gill plate, shown in Figure 7, was introduced in 1990 (28). These new overlap gill air distributors eliminate the need for a fine screen and perform dual functions as efficient air distributor and product retainer. Other advantages claimed by the manufacturer are validatable clean in place (CIP), controlled fluidization, and directional flow of air to discharge the processed product from the container.

Spray Nozzle

A spray is a zone of liquid drops in a gas and spraying is the act of breaking up a liquid into a multitude of these droplets. The general purpose of spraying is to increase the surface area of a given mass of liquid in order to disperse it over the product area. The primary concern is with the increase of surface area per unit mass achieved by spraying. The nozzle is an orifice through which liquid is forced, normally by compressed air. This is

done by three general methods; (1) liquid may be sucked up by a pressure drop created over the nozzle cap, after which compressed air atomizes the liquid stream by disintegrating it with air jets, or (2) the compressed air operates a piston arrangement that pushes the liquid through the orifice and then lets surface tension create droplets or (3) another method of atomizing liquid is to impinge two pressure streams of liquid upon each other, and so form a highly dispersed uniform spray.

The type of spray system is usually characterized by one of four nozzle designs (Fig. 8) (29):

1. *Pressure nozzle*: the fluid under pressure is broken up by its inherent instability and its impact on the atmosphere, on another jet, or on a fixed plate.
2. *Rotating Nozzle*: (rotary atomizer) fluid is fed at low pressure to the center of a rapidly rotating disk and centrifugal force breaks up the fluid. These types of nozzles are used mainly in a spray drying application.
3. *Airless spray nozzle*: the fluid is separated into two streams that are brought back together at the nozzle orifice, where upon impingement, they form drops.
4. *Gas atomizing nozzle* (two-fluid nozzle): the two-fluid (binary) nozzle where the binder solution (first fluid) is atomized by compressed air (second fluid) is the most commonly used nozzle for the fluid-bed granulation (Fig. 9A and B).

These nozzles are available as a single-port or multi-port design. Generally, the single port nozzles are adequate up to 100 kg batch, but for larger size batches a multi-port nozzle such as either a three port (Fig. 10) or six port (Fig. 11) nozzle is required. When these nozzles are air atomized, the

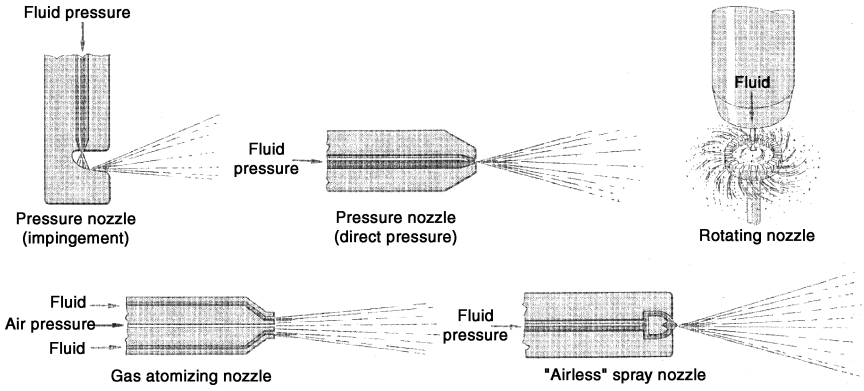

Figure 8 Four types of nozzles. *Source*: From Ref. 29.

(A)

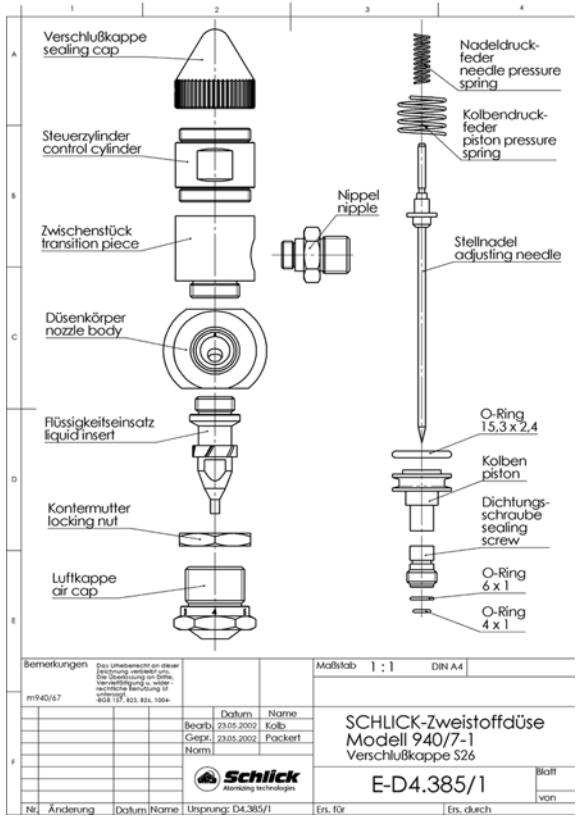

Figure 9 (**A**) Schematic of a nozzle showing different parts. *Source*: Courtesy of Schlick, Germany. (**B**) Schematic of a two-fluid nozzle. (*Continued*)

spray undergoes three distinct phases. In the first, the compressed air (gas) expands, essentially adiabatically, from the high pressure at the nozzle to that of the fluid-bed chamber. The gas undergoes a Joule–Thomson effect, and its temperature falls. In the second phase, the liquid forms into discrete drops. During this atomization, the liquid's specific surface area usually increases 1000 times. In the third phase, the drops travel after being formed, until they become completely dry or impinge on the product particles. During this phase, the solvent evaporates and the diameter of the drops decreases. The energy required to form a drop is the product of the surface tension and the new surface area. About 0.1 cal/g is needed to subdivide 1 g of water into 1 μm droplets. The air pressure required to atomize the binder liquid is set by means of pressure regulator. The spray pattern and spray angle is adjusted by adjusting the air cap.

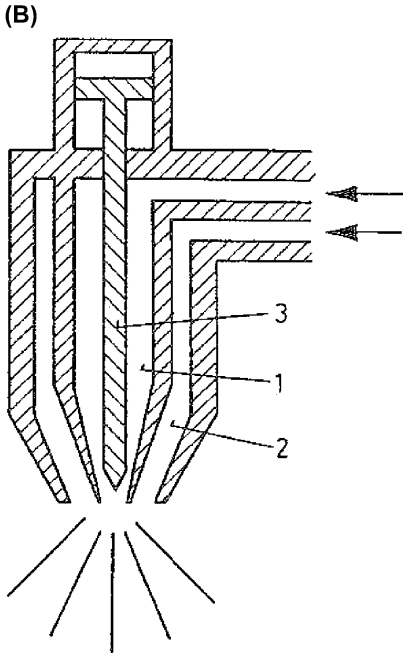

Figure 9B (*Continued*)

Optimum atomization is achieved by fine adjustment of the air cap and atomization air pressure measured at the nozzle. The binder solution is delivered to the nozzle port through a spray lance and tubing. The peristaltic- or positive-displacement pump is commonly used to pump the binder solution. The pneumatically controlled nozzle needle prevents the binder liquid from

Figure 10 Three port nozzle. *Source*: Courtesy of the Glatt Group.

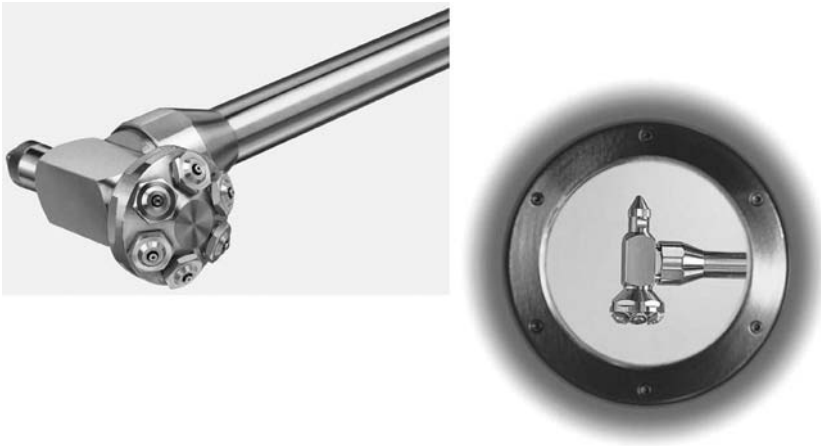

Figure 11 Six port nozzle. *Source*: Courtesy of the Glatt Group.

dripping when the liquid flow is stopped. Nozzle port openings of between 0.8 and 2.8 mm in diameter are most common and are interchangeable.

The two-fluid nozzle in its simplified model is based on energy transmission as shown below:

$$\text{Energy} + \text{Liquid} \longrightarrow \text{Two-fluid nozzle} \longrightarrow \text{Droplets} + \text{Heat}.$$

The ratio of energy dissipation by heat and by the droplet-making process is difficult to measure. Masters (30) suggested that less than 0.5% of applied energy is utilized in liquid-breakup. Virtually the whole amount is imparted to the liquid and air as kinetic energy.

Disengagement Area and Process Filters

Once the air leaves the product bed, fine particles need to be separated from the air stream. Two zones are used in the fluid-bed to separate particles from the air stream: the disengagement area and the exhaust filter. In the disengagement area, larger particles lose momentum and fall back into the bed. The velocity of the process air is highest at the center of the processor and approaches zero at the sidewalls. A process air-filter system removes the particles from the exhaust air. The process air is filtered by using bags or cartridges. The bag filters are widely used and are available as a single bag or with double bag configuration where one bag mechanically shakes the particles, while the other bag remains functional, thus facilitating uninterrupted fluidization. This alternate shaking of dual bags allows the process to be consistent from batch-to-batch. These filter bags can be constructed out of nylon, polyester, polypropylene, and/or polytetrafluroethylene (PTFE) lined materials (Figs. 12 and 13).

Figure 12 Process air bag filter systems. *Source*: Courtesy of the Glatt Group.

To dissipate the potential static charges from the product particles, conductive fabrics are also available and are recommended. Cartridge filters lined with PTFE were introduced to the industry in the 1980s (31). The standard filtration system normally contains a multiple cartridge filter system with an alternating blowback pulse arrangement allowing continuous product fluidization. A cleanable polyester two-micron material is utilized for processing water soluble and non-soluble materials which has electrical conductivity for static-free operation. Recently, cartridges made of stainless steel suitable for CIP have been introduced (32). Various suppliers of the process equipment have optional

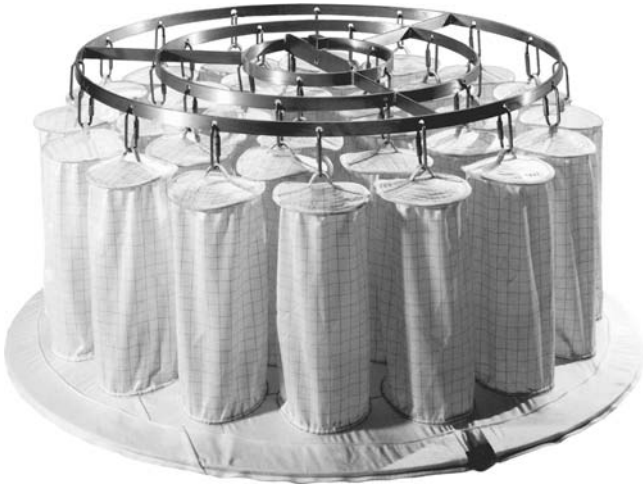

Figure 13 Process air bag filter systems. *Source*: Courtesy of Vector Corporation.

filter arrangements. The vertical filter cartridge claimed to provide better cleaning, however, requires mechanical means to bring the filters down to replace them. Cartridge filters located at an angle provide better access to remove from and replace in the unit. They are equally effective. Figure 14 shows the PTFE cartridge filter arrangements in the fluid-bed processor. The stainless steel cartridge filters (Fig. 15) are an expensive alternative to the cloth filter bags, but provide the possibility of cleaning using an automated CIP system. For a potent compound processing, these cartridge filters with a CIP capability are normally recommended.

During the granulation or drying process, cloth filters are mechanically shaken to dislodge any product which adhered while cartridge filters use a low pressure compressed air blowback system to do the same.

Exhaust Blower or Fan

Once the air leaves the exhaust filters, it travels to the fan. The fan is on the outlet side of the system, which keeps the system at a lower pressure than the surrounding atmosphere. The air flow is controlled by a valve or damper

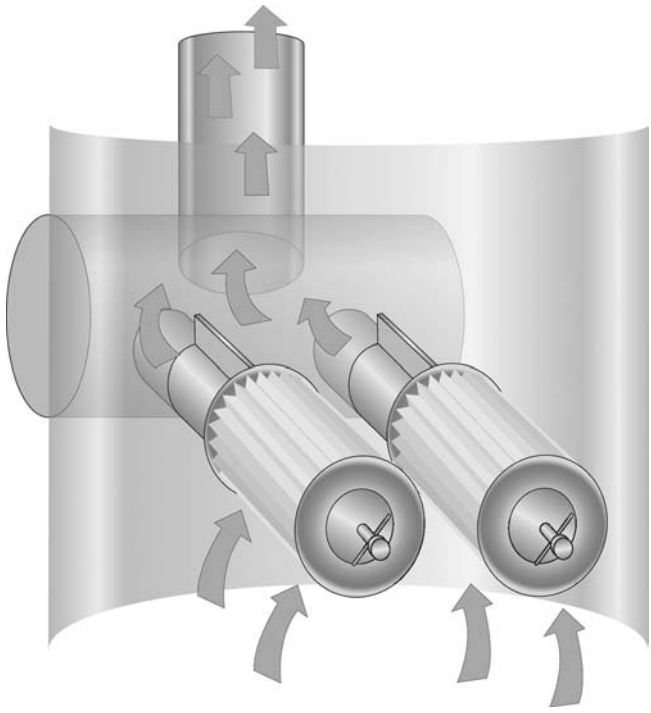

Figure 14 PTFE cartridge filter system. *Source*: Courtesy of Vector Corporation.

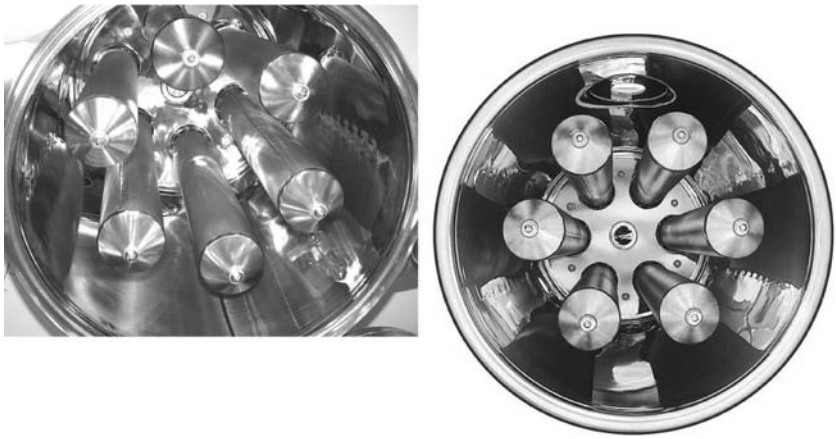

Figure 15 Stainless steel cartridge filters. *Source*: Courtesy of the Glatt Group.

installed just ahead or after the fan. The selection of the fan is normally done by the manufacturer, based upon the layout and complexity of the system. Fan size is determined by calculating the pressure drop (ΔP) created by all the components that make up the fluid-bed processor, including product at the highest design airflow volume.

Control System

A fluid-bed granulation process can be controlled by pneumatic analog control devices, or using state of the art, programmable logic controllers (PLC) or computers. The electronic-based control system offers not only reproducible batches according to the recipe but a complete record and printout of all the process conditions. Process control technology has changed very rapidly and it will continue to change as advances in computer technology take place and as the cost of control systems falls. Near infrared (NlR) technology is routinely used to monitor moisture to control process, which is discussed later in this chapter.

Solution Delivery System

A peristaltic pump capable of delivering binder solution at a controlled rate is desirable. The liquid is transported from the solution vessel through the tubing and atomized, using a two-fluid (binary) nozzle, in the fluid-bed processor.

Laboratory Units

During process development, the supply of active ingredients is scarce. A smaller unit with all of the functionalities of a larger unit is desirable.

Figure 16 Table top unit from Niro. *Source*: Courtesy of Niro Pharma Systems.

The process parameters developed at this stage may not be fully scalable; however, one can process 20 to 100 g of material. Figures 16 and 17 show various smaller size units that can be used for process feasibility and preliminary development work.

PARTICLE AGGLOMERATION AND GRANULE GROWTH

Agglomeration can be defined as the size enlargement process, in which the starting material is fine particles and the final product is an aggregate in which primary particles can still be identified. The granules are held together with bonds formed by the binder used to agglomerate. Various mechanisms of granule formation have been described in the literature (33–35). Three mechanisms for granule formation have been suggested by the researchers. These are:

1. Bridges due to *immobile liquids* form adhesional and cohesional bridging bonds. Thin adsorption layers are immobile and can contribute to the bonding of fine particles under certain circumstances.

Figure 17 Lab unit from Heinen. *Source*: Courtesy of the Heinen Group.

2. *Mobile liquids*, where interfacial and capillary forces are present.
3. *Solid bridges* formed due to crystallization of dissolved substances during drying.

The type of bond formed goes through four transition states, described by Newitt and Conway-Jones (33) as:

1. Pendular
2. Funicular
3. Capillary
4. Droplet (normally happens during spray drying)

Most of the fluid-bed granulated products require much less of an amount of wetting than the high-shear granulation or spray dryer processed product. In the fluid-bed granulation process, the particles are suspended in the hot air stream and the atomized liquid is sprayed on it. The degree of bonding between these primary particles to form an agglomerated granule

depends on the binder used, the physico-chemical characteristics of the primary particles being agglomerated, and upon process parameters.

Schaefer and Worts (36) and Smith and Nienow (37) have reported a description of the growth mechanisms in the fluid-bed, where the bed particles are wetted by liquid droplets in the spray zone. Atomized liquid from the nozzle tends to spread over the particle surface as long as there is an adequate wettability of the particle by the fluid (38). Wet particles on impact form a liquid bridge and solidify as the agglomerates circulates throughout the remainder of the bed. Solid bridges then hold particles together. The strength of the binder determines whether these particles stay as agglomerates. These binding forces should be larger than the break-up forces and, in turn, depend on the size of the solid bridge. The break-up forces arise from movement of the randomized particles colliding with each other and are related to the excess gas velocity and particle size.

Granulation Mechanisms

Four key mechanisms or *rate processes* contribute to granulation, as originally outlined by Ennis (39,40) and later developed further by Litster and Ennis (41). These include *wetting* and nucleation, *coalescence* or growth, *consolidation*, and *attrition* or breakage. Initial *wetting* of the powders and existing granules by the granulating fluid is strongly influenced by spray rate or fluid distribution, as well as product formulation properties, in comparison with mechanical mixing. Wetting promotes *nucleation* of fine powders, or coating in the case of product particle size in excess of droplet size. Often, wetting agents such as surfactants are carefully chosen to enhance poor wetting powders. In the *coalescence* or *growth* stage, partially wetted primary particles and larger nuclei coalesce to form granules composed of several particles. The term *nucleation* is typically applied to the initial coalescence of primary particles in the immediate vicinity of the larger wetting drop, whereas the more general term of *coalescence* refers to the successful collision of two granules to form a new larger granule. In addition, the term of *layering* is applied to the coalescence of granules with primary particles of powders. Nucleation is promoted from some initial distribution of moisture, such as a drop or from the homogenization of a fluid feed to the bed, as with high-shear mixing. The nucleation process is strongly linked with the wetting stage. As granules grow, they are consolidated by compaction forces due to bed agitation. This *consolidation* stage strongly influences *internal* granule voidage or granule porosity, and therefore end-use properties such as granule strength, hardness or dissolution. Formed granules may be particularly susceptible to *attrition* if they are inherently weak or if flaws develop during drying.

These mechanisms or rate processes can occur simultaneously in all processes, ranging from spray drying to fluidized beds to high-shear mixers.

However, certain mechanisms may dominate in a particular process. For example, fluidized bed granulators are strongly influenced by the wetting process, whereas mechanical redispersion of binding fluid by impellers and particularly high-intensity choppers diminish the wetting contributions to granule size in high-shear mixing. On the other hand, granule consolidation is far more pronounced in high-shear mixing than fiuidized bed granulation. These simultaneous rate processes taken as a whole—and sometimes competing against one another—determine the final granule size distribution and granule structure and voidage resulting from a process, and therefore the final end-use or product quality attributes of the granulated product.

If the binding forces are in excess of the break-up forces, either in the wet state or in the dry state, uncontrolled growth will proceed to an overwetted bed or production of excessive fines, respectively. If a more reasonable balance of forces is present, controlled agglomeration will occur, growth of which can be controlled. Maroglou and Nienow presented a granule growth mechanism in the fluid-bed by the use of model materials and scanning electron microscope (42). Figure 18 shows the various paths a liquid droplet can take and its consequences on the particle growth.

The mechanism of formation of a granule and, its subsequent growth primarily progresses through three stages:

1. Nucleation
2. Transition
3. Ball growth

Figure 19 shows the growth of the granule relative to the liquid added. In the beginning of the spraying stage, primary particles form nuclei and are held together by liquid bridges in a pendular state. The size of these nuclei depends upon the droplet size of the binder solution. As the liquid addition continues, more and more nuclei agglomerate and continue the transition from the pendular state to the capillary state.

The uniqueness of the fluid-bed agglomeration process is the way the liquid addition and drying (evaporation) steps are concurrently carried out. When the granulation liquid is sprayed into a fluidized bed, the primary particles are wetted and form, together with the binder, relatively loose and very porous agglomerates. Densification of these agglomerates is brought about solely by the capillary forces present in the liquid bridges. It is therefore important that the quantity of liquid sprayed into the bed should be relatively large compared with that used in high-shear granulation. Drying a wet product in a fluid-bed is a separate topic, but during the fluid-bed granulation process, it becomes an integral part of the process, hence, understanding fluid-bed drying is important before we review the agglomeration process.

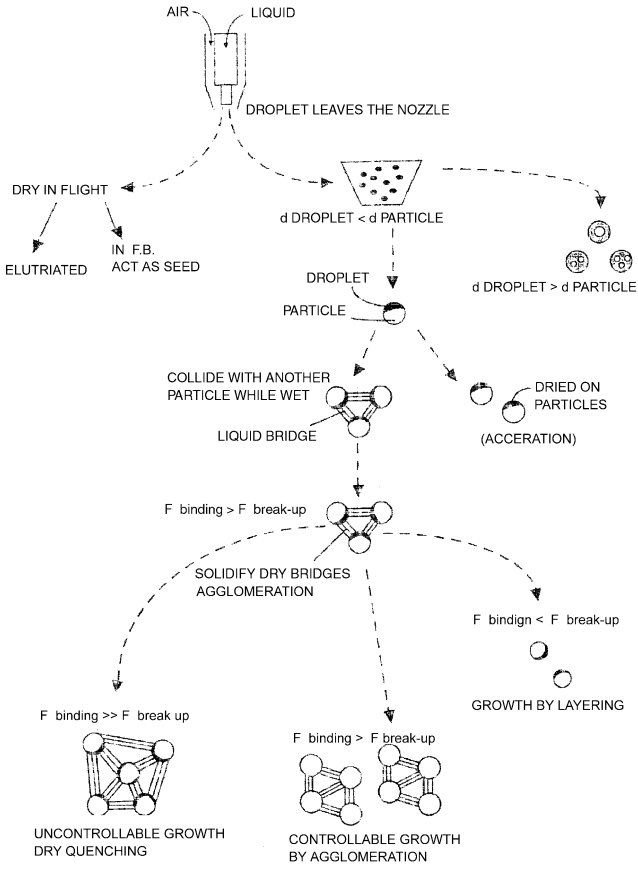

Figure 18 Mechanism of granulation in fluid-bed. *Source*: Adapted from Ref. 43.

FLUID-BED DRYING

Drying is usually understood to be removal of moisture or solvent. Drying involves heat transfer and mass transfer. Heat is transferred to the product to evaporate liquid, and mass is transferred as a vapor in the surrounding gas; hence, these two phenomena are interdependent. The drying rate is

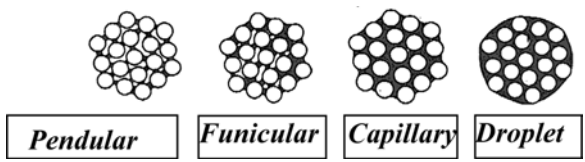

Figure 19 States of liquid saturation. *Source*: Adapted from Barlow.

determined by the factors affecting the heat and mass transfer. The transfer of heat in the fluid-bed takes place by convection. Convection is the transfer of heat from one point to another within a fluid (gas, solid, and liquid) by the mixing of one portion of the fluid with another. The removal of moisture from a product granulated in the fluid-bed granulator or in other equipment essentially removes the added water or solvent. This *free moisture content* is the amount of moisture that can be removed from the material by drying at a specified temperature and humidity. The amount of moisture that remains associated with the material under the drying conditions specified is called the *equilibrium moisture content*, or *EMC*.

The evaporation rate of liquid film surrounding the granule being dried is related to the rate of heat transfer by the equation

$$dw/dt = hA/H\ \partial T$$

where dw/dt is the mass transfer rate (drying rate), h is the heat transfer coefficient, A is the surface area, H the latent heat of evaporation, and ∂T is the temperature difference between the air and the material surface.

Because fluid-bed processing involves drying of a product in suspended hot air, the heat transfer is extremely rapid. In a properly fluidized processor, product temperature and the exhaust air temperatures should reach equilibrium. Improper air distribution, hence poor heat transfer in a fluidized bed, cause numerous problems, such as caking, channeling, or sticking. The capacity of the air (gas) stream to absorb and carry away moisture determines the drying rate and establishes the duration of the drying cycle. Controlling this capacity is the key to controlling the drying process. The two elements essential to this control are inlet air temperature and air flow. The higher the temperature of the drying air, the greater its vapor holding capacity. Since the temperature of the wet granules in a hot gas depends on the rate of evaporation, the key to analyzing the drying process is psychrometry (44–46).

Psychrometry is defined as the study of the relationships between the material and energy balances of water vapor–air mixture. Psychrometric charts (Fig. 20) simplify the crucial calculations of how much heat must be added and how much moisture can be added to the air. The process of drying involves both heat and mass transfer. For drying to occur, there must be a concentration gradient which must exist between the moist granule and the surrounding environment. As in heat transfer, the maximum rate of mass transfer that occurs during drying is proportional to the surface area, turbulence of the drying air, the driving force between the solid and the air, and the drying rate. Because the heat of vaporization must be supplied to evaporate the moisture, the driving force for mass transfer is the same driving force required for heat transfer, which is the temperature difference between the air and the solid.

Schaefer and Worts (47) have shown that the higher the temperature differences between incoming air and the product, the faster the drying rate.

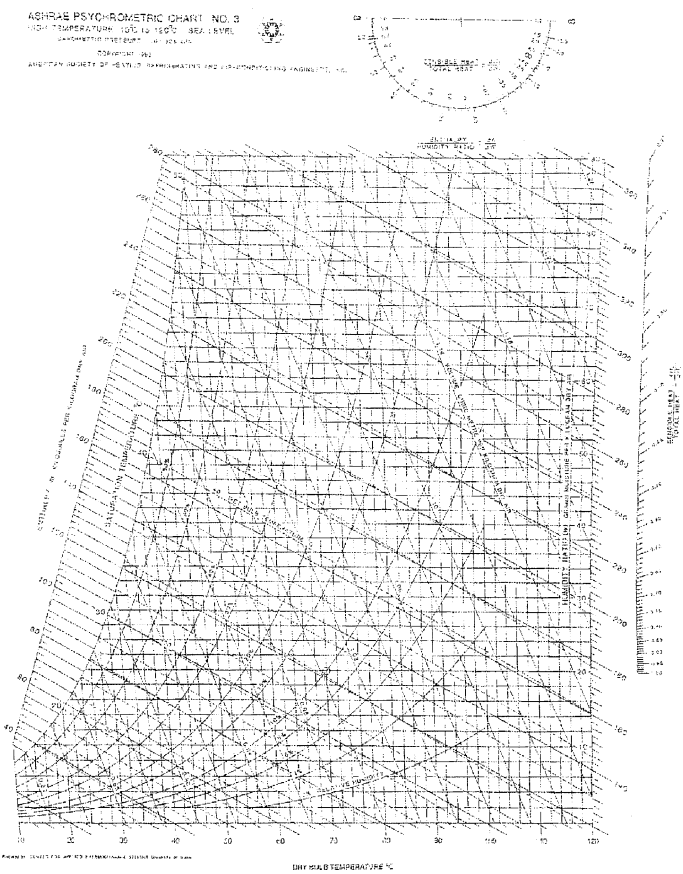

Figure 20 Psychrometric chart.

Therefore, product temperature should be monitored closely to control the fluidized bed drying process. During fluid-bed drying, the product passes through three distinct temperature phases (Fig. 21). At the beginning of the drying process, the material heats up from the ambient temperature to approximately the wet-bulb temperature of the air in the dryer. This temperature is maintained until the granule moisture content is reduced to the critical level. At this point, the material holds no free surface water, and the temperature starts to rise further.

The drying capacity of the air depends upon the relative humidity (RH) of the incoming air. At 100% RH, the air is holding the maximum amount of water possible at a given temperature, but if the temperature of the air is raised, the relative humidity drops and the air can hold more moisture. If air is saturated with water vapor at a given temperature, a drop in temperature will force the air mass to relinquish some of its moisture

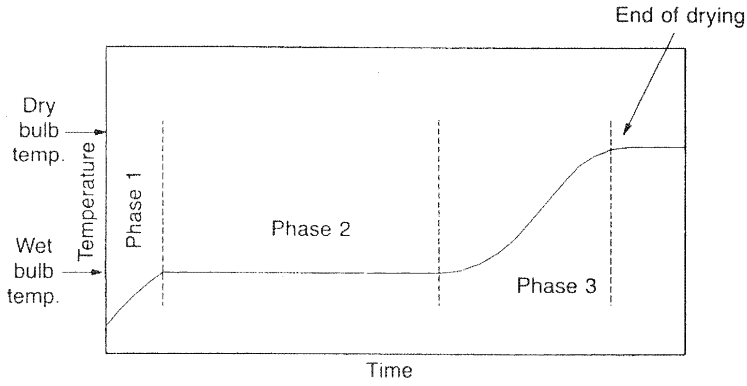

Figure 21 Product temperature changes during drying in a fluid-bed processor. *Source*: From Ref. 20.

through condensation. The temperature at which moisture condenses is the dew point temperature. Thus, the drying capacity of the air varies significantly during processing. By dehumidifying the air to a preset dew point, incoming air can be maintained at a constant drying capacity (dew point), and hence provide reproducible process times.

PROCESS AND VARIABLES IN GRANULATION

Granulation Process

As with any granulating system in fluid-bed granulation processing, the goal is to form agglomerated particles through the use of binder bridges between the particles. To achieve a good granulation, particles must be uniformly mixed, and liquid bridges between the particles must be strong and easy to dry. Therefore, this system is sensitive to the particle movement of the product in the unit, the addition of the liquid binder and the drying capacity of the air. The granulation process in the fluid-bed requires a binary nozzle, a solution delivery system, and compressed air to atomize the liquid binder.

Thurn (48), in a 1970 thesis, investigated details of the mixing, agglomerating and drying operations which take place in the fluid-bed process. Results indicated that the mixing stage was particularly influenced by air flow rate and air volume. It was suggested that the physical properties of the raw materials, such as hydrophobicity, may exert a strong influence upon the mixing stage. At the granulation stage, particular attention was paid to the nozzle and it was concluded that a binary design (two-fluid) nozzle gave a wide droplet size distribution yielding a homogeneous granule. The need for strong binders was recommended to aid granule formation and it was suggested that the wettability of the raw materials required particular attention. Several research papers have been published on the influence of raw

material (47–64), binder type (5,8,47,48,58,60,65–75), binder concentration and binder quantity (8,51,56,60,62,65,67–69,72–74,76–92).

Each phase of the granulation process must be controlled carefully to achieve process reproducibility. When binder liquid is sprayed into a fluidized bed, the primary particles are wetted and form, together with the binder, relatively loose and very porous agglomerates. Densification of these agglomerates is brought about almost solely by the capillary forces present in the liquid bridges. It is therefore important that the liquid binder sprayed into the bed should be relatively large in quantity compared with that used in high- or low-shear granulation process. During spraying, a portion of the liquid is immediately lost by evaporation, so the system has little tendency to pass beyond the liquid bridge phase. The particle size of the resulting granule can be controlled to some extent by adjusting the quantity of binder liquid and the rate at which it is fed, i.e., the droplet size. The mechanical strength of the particles depends principally on the composition of the primary product being granulated and the type of the binder used. Aulton et al. (82) found that lower fluidizing air temperature, a dilute solution of binder fluid, and a greater spray rate produced better granulation for tabletting.

Variables

Factors affecting the fluid-bed granulation process can be divided into three broad categories:

- Formulation-related variables
- Equipment-related variables
- Process-related variables

Formulation-Related Variables

Properties of primary material: Ideally, the particle properties desired in the starting material include a low particle density, a small particle size, a narrow particle size range, a particle shape approaching the spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing. Properties such as cohesiveness, static charge, particle size distribution, crystalline or amorphous nature, and wettability are some of those which have impact on the type of granules formed. The cohesiveness and static charges on particles present fluidization difficulty. The same difficulties were observed when the formulation contained hydrophobic material or a mixture of hydrophilic and hydrophobic materials. The influence of hydrophobicity of primary particles has been shown by Aulton and Banks (17), where they demonstrated that the mean particle size of the product was directly related to wettability of the primary particles expressed as $\cos\theta$ (where θ is the contact angle of the particles). It was also reported that as the hydrophobicity of the mix is increased, a decrease in granule growth is observed. Aulton, Banks, and Smith, in a later publication,

showed that addition of a surface active agent, such as sodium laurel sulfate, improves the fluidized bed granulation (64). In a mixture containing hydrophobic and hydrophilic primary particles, granule growth of hydrophilic materials takes place selectively, creating content uniformity problems. Formulating a controlled release granulation can be accomplished by using fluid-bed granulation. A controlled release matrix formulation of naproxen was successfully developed using fluid-bed granulation (93).

Low-dose drug content: Wan et al. (94) studied various methods of incorporating a low-dose drug such as chlorphenarmine maleate in lactose formulation with PVP as the granulating solution. They concluded that the randomized movement of particles in the fluid-bed may cause segregation of the drug and that uniform drug distribution was best achieved by dissolving the drug in a granulating solution. The mixing efficiency of drug particles with the bulk material was found to increase in proportion to the granulating liquid used to dissolve the drug. The optimum nozzle atomizing pressure was deemed to be important to avoid spray drying the drug particles or overwetting, which creates uneven drug distribution. Higashide et al. (95) studied the fluidized bed granulation using five-fluorouracil in a concentration of 0.3% in 1:1 mixture of starch and lactose. Hydroxy propyl cellulose (HPC) was used as the binder. The ratios of starch and lactose contained in the granules were measured gravimetrically. The researchers discovered that a bigger amount of the drug and starch was found in larger granules than in smaller granules. The results were attributed to the hydrophobicity of the five-fluorouracil, starch and the hydrophilicity of lactose.

Binder: Different binders have different binding properties and the concentration of an individual binder may have to be changed to obtain similar binding of primary particles. Thus, the type of binder, and binder content in the formulation and concentration of the binder have major influence on granule properties. These properties include friability, flow, bulk density, porosity, and size distribution.

Davies and Gloor (96,97) reported that the types of binder, such as povidone, acacia, gelatin, and hydroxypropyl cellulose (HPC), all have different binding properties that affect the final granule properties mentioned above. Hontz (90) investigated microcrystalline cellulose concentration, inlet air temperature, and binder (PVP) concentration and binder solution concentration effects on tablet properties. Binder and microcrystalline cellulose concentration were found to have significant effect on tablet properties. Alkan and Ulusoy (75) studied binder (PVP) addition in solution and as a dry powder in the powder mix. They found a larger mean granule size when the dry binder was granulated with ethanol. However, when the binder was in a solution, the granules produced were less friable and more free flowing. This same finding was confirmed by other researchers (91,92). Binder temperature affects the viscosity of the solution and, in turn,

affects the droplet size. Increased temperature of the binder solution reduces the viscosity of the solution, reducing the droplet size and hence producing smaller mean granule size. Binder solution viscosity and concentration affect the droplet size of the binder. Polymers, starches, and high molecular weight PVP cause increased viscosity, which, in turn, creates larger droplet size and, subsequently, larger mean granule particle size (67).

Diluted binders are preferred because they facilitate finer atomization of the binder solution, provide control of the particle size, reduce friability and increase the bulk density, even though the tackiness or binding strength may suffer (8,68,78,82,82,97).

Binder solvent: In most instances, water is used as a solvent. The selection of solvent, such as aqueous or organic, depends upon the solubility of the binder and the compatibility of product being granulated. Generally organic solvents, due to their rapid vaporization from the process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization as shown in Table 1. The requirement of solvent for the binder can be eliminated by incorporating binder or mixture of binders of low melting point with the drug substance in the dry form. The temperature of the incoming air is sufficient to melt the binder and form the granules.

Equipment-Related Variables

Design: The availability of the fluid-bed processors from different suppliers of the equipment is essentially similar. The differences in design of different suppliers sometimes provide difficulty in scaling-up from the laboratory units to production units in a linear scale.

To fluidize and thus granulate and dry the product, a certain quantity of process air is required. The volume of the air required will vary, based upon the amount of material that needs to be processed. The ratio of drying capacity of the process air and quantity of the product needs to be maintained constant throughout the scaling-up process. However, some suppliers of the equipment provide higher drying capacity for their laboratory unit

Table 1 Heat of Vaporization for Commonly Used Solvents

Solvent	Solvent boiling point (°C)	Density (g/mL)	Heat of vaporization (kcal/g)
Methylene chloride	40.0	1.327	77
Acetone	56.2	0.790	123.5
Methanol	65.0	0.791	262.8
Ethanol	78.5	0.789	204.3
Isopropanol	82.4	0.786	175.0
Water	100.0	1.000	540.0

but cannot maintain the same ratio for the production units. This lack of proportionality reduces the drying capacity per unit volume of the process air, resulting in longer process time in the production units. The current design of the fluid-bed is a modular one, where multiple processes such as drying, granulating, coating, rotary processing, etc., can be carried out by simply changing the container specially designed for the process.

Air distributor: The process of agglomeration and attrition due to random fluidization requires control of the particle during the granulation process. Optimization of the process requires control over fluidized particles. This is a complex phenomenon due to the prevailing fluidizing conditions and a particle size distribution which undergoes changes during the process. As the conditioned air is introduced through the lower plenum of the batch fluid-bed, the fluidizing velocity of a given volume of air determines how fluidization will be achieved.

Perforated air distributor plates covered with the 60–325 mesh fine stainless steel screen, described previously, provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air distributor plates that have a 4–30% open area are normally available. These interchangeable plates provide a range of loading capacities so that batches of various sizes can be produced efficiently and with uniform quality. To prevent channeling, an operator can select a plate with optimum lift properties. For example, a product with low bulk density requires low fluidizing velocity. A distributor plate having a small open area to give a large enough pressure drop may provide uniform fluidization of such a product without reaching entraining velocity and impinging the process filters. Alternatively, a product with higher bulk density can be fluidized and processed using a plate with a larger open area. The air distributor plate consists of a perforated plate and a fine mesh screen. This arrangement sometimes causes problems like product leakage, due to a torn screen, and difficulty in cleaning without separating the perforated plate and the fine mesh screen. To overcome these deficiencies, an overlap gill plate has been recently introduced. These plate designs were discussed earlier in the chapter.

Pressure drop: Flow of air through the fluid-bed processor is created by the blower or a fan located downstream from the process chamber. This fan imparts motion and pressure to air using a paddle-wheel action. The moving air acquires a force or pressure component in its direction of motion because of its weight and inertia. This force is called velocity pressure and is measured in inches or millimeters of water column. In operating duct systems, a second pressure that is independent of air velocity or movement is always present. Known as static pressure, it acts equally in all directions. In exhaust systems, such as fluid-bed processors, a negative static pressure exists on the inlet side of the fan. Total pressure is thus a combination of static and velocity pressures. Blower size is determined by calculating

the pressure drop (∂P) created by all the components of the fluid-bed processing system. Proper selection of a blower is essential in fluid-bed design. A blower with appropriate ∂P will fluidize the process material adequately. However, a blower without enough ∂P will not allow proper fluidization of the product, resulting in longer process time and improper granulation. A similar effect can be seen when a product with unusually high bulk density is processed in place of normal pharmaceutical materials, or an air distributor plate offers high resistance due to its construction. This creates a pressure drop that the blower was not designed to handle. A proper sized blower or fan should develop sufficient ∂P so that the exhaust damper can be used in the 30–60% open position. Any additional components, such as scrubbers, exhaust HEPA, police filters or additional components in the air handling unit, would require a larger blower/static pressure which can be recommended by the supplier of the fluid-bed processor.

Filters: To retain entrained particles of a process material, process filters are used. To maintain these filters from building up layers of fine process material, and causing higher pressure drop and thus improper fluidization, these filters are cleaned during the granulation process. When bag filters are used, mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation of airflow and, thus, interrupting of fluidization during the filter cleaning process. In units with a single bag house, this results in a momentary *dead bed*, where no fluidization takes place. This interruption in the process extends the process time. To avoid process interruptions, a multi-shaking filter bag arrangement is desired, where granulation process is continuous. The continuous process is also achieved by using bag filters with a blow back or using stainless steel filter bags where air under pressure is pulsed through the filters. Generally, filters should be cleaned frequently during the granulation step, so as to incorporate the fines in the granulation. This is possible if the cleaning frequency is high and the period between the filter cleanings is short. Rowley (98) reported the effect of bag-shake/interval cycle. He discussed the possibility of improving particle size distribution by optimizing the shake time and the corresponding interval between bag shakes.

The following general guidelines for filter cleaning frequency and duration are recommended.

Single shaker unit: frequency-2–10 minutes between filter cleaning, 5–10 seconds for shaking. This may vary as the fine powders form granules and the frequency between the shakes or duration of shaking interval can be extended. In any case, the dead bed time should be kept at a minimum in a single shaker unit.

Multiple shaker unit: since this is a continuous process, frequency of shaking for each section is approximately 15–30 seconds between filter

cleanings, and about five seconds for shaking the filters. If a low pressure blow back system is used for the bags, the frequency of cleaning is about 10–30 seconds.

Cartridge filter: these offer continuous processing and require cleaning frequency of 10–30 seconds. The cleaning frequency and cleaning duration is now offered as an automated system where, instead of having to base the cleaning frequency on time, the trigger point for filter cleaning is the build up of a pressure drop across the filters. This automates the process and eliminates operator input.

Miscellaneous factors: Product bowl geometry is considered to be a factor that may have impact on the agglomeration process. The fluidization velocity must drop from the bottom to the top rim of the bowl by more than half to prevent smaller, lighter particles being impinged into the filter, creating segregation from heavier product components in the bowl. Generally, a conical shape of the container and expansion chamber is preferred where the ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multi-processor concept where a single unit can be used for drying, agglomerating, air suspension coating or rotary processing by changing the processing container while the rest of the unit is common. This approach does eliminate the concerns about the geometry of the processor because of the way these units are constructed.

Process-Related Variables

The agglomeration process is a dynamic process where a droplet is created by a two-fluid nozzle, and deposited on the randomly fluidized particle. The binder solvent evaporates, leaving behind the binder. Before all of the solvent is evaporated, other randomized particles form bonds on the wet site. This process is repeated numerous times to produce desired agglomerated product. There are number of process variables that control the agglomeration. Process variables most important to consider are listed as follows:

1. process inlet air temperature
2. atomization air pressure
3. fluidization air velocity and volume
4. liquid spray rate
5. nozzle-position and number of spray heads
6. product and exhaust air temperature
7. filter porosity and cleaning frequency, and
8. bowl capacity

These process parameters are interdependent and can produce desirable product if this interdependency is understood. Inlet process air temperature is determined by the choice of binder solvent, whether aqueous or organic, and

the heat sensitivity of the product being agglomerated. Generally, aqueous solvent will enable the use of temperatures between 60°C and 100°C. On the other hand, organic solvent will require the use of temperatures from 50°C to below room temperature. Higher temperature will produce rapid evaporation of the binder solution and will produce smaller, friable granules. On the other hand, lower temperature will produce larger, fluffy and denser granules. Figure 22 shows the relationship of inlet and product air temperature and outlet air humidity during the granulation process.

The process of drying while applying spraying solution is a critical unit operation. This mass transfer step was previously discussed. The temperature, humidity and volume of the process air determine the drying capacity. If the drying capacity of the air is fixed from one batch to the next, then the spray rate can also be fixed. If the drying capacity of the air is too high, the binder solution will have a tendency to spray dry before it can effectively form bridges between the primary particles. If, on the other hand, the drying capacity of the air is too low, the bed moisture level will become too high and particle growth may become uncontrollable. This will result in unacceptable movement of the product bed.

As previously discussed, the appropriate process air volume, inlet air temperature and binder spray rate are critical to achieving proper and con-

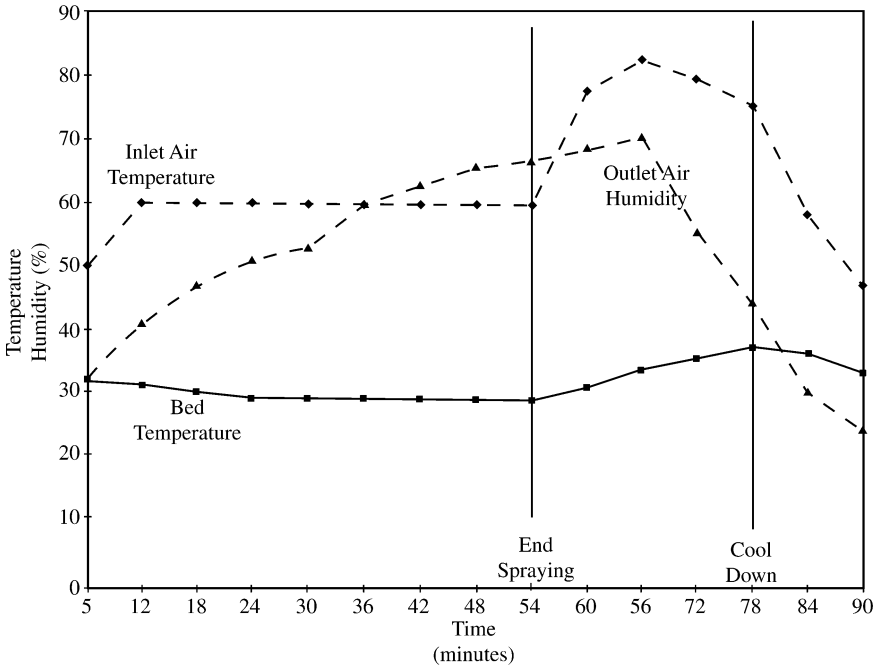

Figure 22 Temperature and humidity versus time for spray granulation process.

sistent particle size distribution and granule characteristics. There are many ways to arrive at the proper operating parameters. The following procedure was found by the author to be one of the ways one can set the operating parameters when granulating with fluid-bed processors:

1. Determine the proper volume of air to achieve adequate mixing and particle movement in the bowl. Avoid excessive volumetric airflow so as to entrain the particles into the filters.
2. Choose an inlet air temperature that is high enough to negate weather effects (outside air humidity or inside room conditions). The air temperature should not be detrimental to the product being granulated. (To achieve consistent process year round, a dehumidification/humidification system is necessary, which provides the process air with constant dew point and, hence, constant drying capacity.)
3. Achieve a binder solution spray rate that will not dry while spraying (spray drying) and will not overwet the bed. This rate should also allow the nozzle to atomize the binder solution to the required droplet size.
4. As stated earlier, a typical air velocity used for spray granulation is from 1.0 m/sec to 2.0 m/sec.

Table 2 is based upon the psychrometric chart which gives a first guess at determining the proper spray rate for a spray granulation process in a fluid-bed processor. Table 2 shows the relationship between the air flow and binder spray rate and inlet air temperature which can be used as a starting point to set process parameters when considering the fluid-bed granulation process.

Variables in the fluid-bed granulation process and its impact on the final granulation were summarized by Davies and Gloor Jr (99), where they state that the physical properties of granulation are dependent upon both the individual formulations and the various operational variables associated with the process. The solution spray rate increase and subsequent increase in average granule size resulted in a less friable granulation, higher bulk density and a better flow property for a lactose/corn starch granulation. Similar results were obtained by an enhanced binder solution, decreasing nozzle air pressure, or lowering the inlet-air temperature during the granulation cycle. The position of the binary nozzle with respect to the fluidized powders was also studied. It was concluded that by lowering the nozzle, binder efficiency is enhanced, resulting in average granule size and a corresponding decrease in granule friability. The significant process parameters and their effect on the granule properties are summarized in Table 3. Maroglou (43) listed various parameters affecting the type and rate of growth in batch fluidized granulation (Table 4A and B) and showed the influence of process parameters and the material parameters on the product.

Table 2 Calculation of Fluid-Bed Spray Rate

Given Process Data
- Air volume range
  - Minimum (1.2 m/s) _____ m^2/hr
  - Maximum (1.8 m/s) _____ m^3/hr
- Inlet air temperature and humidity to be used _____°C_____%RH
- Percentage of solids in sprayed solution _____% solids

From Psychometric Chart
- Air density at point where air volume is measured _____ m^2/kg air
- Inlet air absolute humidity (H) _____ g H2O/kg air
- Maximum outlet air absolute humidity (H) _____ g H2O/kg air (follow line of constant adiabatic conditions)
- Use 100% outlet RH for spray granulator or 30–60% RH (as required for column coating)

Calculations for Spray Rate
- Step 1. Convert air volumetric rate to air mass rate
  - Minimum _____ m^2/hr ÷ (60×_____ m^2/kg air) = _____ kg air/min
  - Maximum_____ m^3/hr ÷ (60×_____ m^3/kg air) = _____ kg air/min
- Step 2. Subtract inlet air humidity from outlet air humidity
  _____(g H2O/kg air) H out ↑ _____(g H2O/kg air) H in
  = _____g H2O removed /kg air
- Step 3. Calculate (minimum and maximum) spray rate of solution.
  This will provide range of generally acceptable spray rates based on the airflow used in the unit

Step 1 (Minimum) _____× step 2 _____ ÷ [1 − (_____% solids ÷100]
= _____spray rate g/min) at minimum air flow

Step 2 (Maximum) _____× step 2 _____ ÷ [1 − (_____% solids ÷100]
= _____spray rate g/min) at minimum air flow

PROCESS CONTROLS AND AUTOMATION

The agglomeration process is a batch process and accurate repeatable control of all critical process parameters is necessary for a robust system. Earlier designs of the fluid-bed processor used pneumatic control, which provided safe operation in hazardous areas but relied heavily on human actions to achieve repeatable product quality and accurate data acquisition. Current designs use PLCs and personal computers (PCs) to achieve sophisticated control and data acquisition. The operating conditions are controlled to satisfy parameters of multiple user-configured recipes and critical data is collected at selected time intervals for inclusion in an end-of-batch report. Access to all user-configured data is protected by security levels with passwords permitting access only to selected functions. With the appropriate security level, not only are operating conditions configured, but also

Table 3 Significant Variables and Their Impact on the Fluid-Bed Granulation Process

Process parameter	Impact on process	References
1. Inlet air temperature	Higher inlet temperature produces finer granules and lower temperature produces larger, stronger granules	72,83
2. Humidity	Increase in air humidity causes larger granule size, longer drying times	37
3. Fluidizing air flow	Proper air flow should fluidize the bed without clogging the filters. Higher air flow will cause attrition and rapid evaporation, generating smaller granules and fines	17,20.72
4. Nozzle and position	A binary nozzle produces the finest droplets and is preferred. The size of the orifice has an insignificant effect except when binder suspensions are to be sprayed. Optimum nozzle height should cover the bed surface. Too close to the bed will wet the bed faster, producing larger granules, while too high a position will spray dry the binder, create finer granules, and increase granulation time	57
5. Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass-to-liquid ratio must be kept constant to control the droplet size and hence the granule size. Higher liquid flow rate will produce larger droplet and larger granules and the reverse will produce smaller granules. At a given pressure an increase in orifice size will increase droplet size	37,57,85,92
6. Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules	17,54,71, 72,92

identification of each valid recipe and operator is entered. The identification is verified before any operator actions are permitted and is included with the end-of-run report. The use of computer related hardware requires some additional validation, but with coordination between the control system provider and the end user, the validation of software can be managed. Figure 23 shows a PLC-based control panel.

The most important sensors for control of the drying process are inlet- and exhaust-air temperature and sensors for airflow measurement, located in the air-transport system. Other sensors for the spray agglomeration process are, atomization air pressure and volume, pressure drops (across the inlet

Table 4 A and B Influence of Operating and Material Parameters on the Granulated Product

A. Operating parameters	Droplet size	NAR[a]
		Atomization air velocity
		Rheology
		Surface tension
		Nozzle position
		Nozzle type
	Bed moisture content	Solution type and feed rate
		Bed temperature
		Fluidization velocity
		Aspect ratio
		Nozzle position and atomization
		Velocity
		Air distributor design
		Jet grinding
	Binder solution/suspension concentration	Bridge strength and size
		Rheology
B. Material parameters	Binder solution/suspension concentration	Bridge strength and size
		Rheology
	Type of binder	Molecular length and weight
	Wettability	Particle–solvent interaction
		Surface tension
		Viscosity
	Material to be granulated	Average particle size
		Size distribution[a]
		Shape and porosity
		Drying characteristics
		Density and density differences[b]

[a]NAR is the ratio of air to liquid flow rates through the nozzle of a twin fluid atomizer expressed either in mass units or in volume units (air at STP).
[b]Especially important relative to elutriation and segregation.

filter), the product container with the product being processed and outlet process air filter, inlet air humidity or dew point, process filter cleaning frequency and duration, spray rate for the binder solution and total process time.

All of these sensors provide constant feed-back information to the computer. These electronic signals may then be stored in the computer's memory and recalled as a batch report. With this ability to recall data analysis, a greater insight can be gained into the process.

The degree of the instrumentation of pharmaceutical unit operations has increased. This instrumentation provides information of the state of the process and can be used for both process control and research. A central part of optimizing production is increasing the level of automation. Besides

Figure 23 PLC-based control panel. *Source*: Courtesy of Niro Pharma Systems.

monitoring the process parameters, a number of approaches is being developed for measuring the moisture of the product to determine the end point of the process and, consequently, the in-process particle size analysis. A numbers of publications discuss on-line moisture measurement and process end point determination using NIR.

Near-Infrared (NIR)

The non-destructive character of vibrational spectroscopy techniques, such as NIR, makes them novel tools for in-line quality assurance (100). NIR has been widely used for the measurement of water in various applications (101). NIR can be applied for both quantitative analysis of water and for determining the state of water in solid material. This gives a tool for understanding the physicochemical phenomena during manufacture of pharmaceutical granulation.

The history of NIR dates back to the studies by Herschel in 1800. The modern NIR analysis was developed in 1950 by the works of a group at USDA (U.S. Department of Agriculture), headed by Karl Norris (101).

Other branches of the chemical industry have also applied NIR for various applications. One feature of NIR is that the applications have been ahead of theoretical aspects. This has hindered the general approval of NIR in the pharmaceutical industry. However, the pharmacopoeias have defined some characteristics of analysis with NIR (102,103). The NIR spectrum is just above the visible region of electromagnetic spectrum (EMS). The NIR region covers the interval between 4000–12,500/per cm (0.8–2.5μm). Molecules that absorb NIR energy vibrate in two fundamental modes: stretching and bending. Stretching is a continuous change in the inter-atomic distance along the axis between two atoms and it occurs at lower wavelengths than bending vibration. A bending vibration is a change in the bond angle between diatomic molecules. A band observed at 1940 nm is known to be caused by O–H stretching and bending vibrations and is the most used analytically (104,105). It has recently been reported, from measurements on silica gel layers, that water content has an effect on NIR absorption at all wavelengths, even where water was absorbed minimally (106). For a solid sample, the reflected light is usually the parameter measured in NIR spectroscopy known as diffuse reflectance. The reflected light consists of two components: specular and diffuse. The specular or mirror-like component in the boundary between two media occurs at the sample surface and it contains little information about the chemical composition of the substance. The NIR spectroscopy is particularly based on the diffused component of the reflected light and it can be affected by particle size and shape distribution, bulk density surface characteristics and temperature (107,108). This portion of the EMS has for the last 30 years been studied and investigated in great detail as a tool for the analysis of many natural and man-made materials (107,109–112).

Developing a functional automation system requires new measuring techniques; new in-line measuring devices are needed (113–117). Solid–water interactions are one of the fundamental issues in the pharmaceutical technology. State of water in solid material may be characterized using X-ray diffraction, microscopic methods, thermal analysis, vibrational spectroscopy, and nuclear magnetic resonance spectroscopy (118). Traditionally, the control of fluidized bed granulation was based on indirect measurements. These control methods were applied to utilize the properties of process air by Schaefer and Worts (47). Frake et al. (119) demonstrated the use of NIR for in-line analysis of the moisture content in 0.05–0.07 mm pellets during spray granulation in fluid-bed processor. Rantanen et al. (120,121) described a similar approach for moisture content measurement, using a rationing of 3–4 selected wavelengths. He and his co-workers

reported that the critical part of in-line process was the sight glass for probe positioning that was continuously blown with heated air. They also reported spectra baselines caused by particle size and refractive properties of the in-line samples; they continued to analyze several data pretreatments to eliminate these effects on their fixed wavelength set-up. Solvents other than water have also been evaluated for real-time quantification.

On-line measurement has also been possible, enabling monitoring of film coating on pharmaceutical pellets in an industrial manufacturing process. Andersson et al. (122) conducted measurements on solid coated tablets, using, a fiber-optic probe positioned in fluid-bed processor. In this case, they secured a representative sampling during processing by using a sample collector that was emptied with compressed air inside the processor. Vazquez recently provided a comprehensive review of FT-NIR application in measuring fluid-bed drying end (123). Rantanen et al. (124) used NIR to monitor moisture as well as airflow. Using in-line multi-channel NIR, the multivariate process data collected was analyzed, using principal component analysis (PCA). The authors showed that robust process control and measurement system, combined with reliable historical data storage, can be used for analyzing the fluid-bed granulation process. PCA modeling proved a promising tool to handle multidimensional data that was collected and for reduction of the dimensionality of process data. FT-NIR spectra gave useful information for understanding the phenomenon during granulation. Rantanen et al. (125) further studied the application of NIR for fluid-bed process analysis. The authors used NIR to study moisture measurement combined with temperature and humidity measurements. By controlling the water during the fluid-bed granulation, the granulation process also was controlled. They concluded that the varying behavior of formulations during processing can be identified in a real-time mode. Thus, they found that NIR spectroscopy offered unique information of granule moisture content during all phases of granulation.

PROCESS SCALE-UP

Overview

As previously discussed, granule growth includes the coalescence of existing granules which have been wetted by binder spray and nucleation. As granules grow, they are simultaneously compacted by consolidation mechanisms that reduce internal voidage or porosity. Various growth patterns were discussed previously; the prevailing mechanisms are dictated by a balance of critical particle level properties that control formulation deformability, and operating variables that control the localized level of shear, or bed agitation intensity. In a fluid-bed, little deformation takes place during granule collision during granulation. Growth is generally controlled by the extent of any surface fluid layer and surface deformability.

To obtain uniform granules, one has to start with product approaching a uniform state of mixing, which, in turn, will ensure equal moisture and shear levels and therefore uniform granulation kinetics throughout the bed. For scale-up, one must account for this fact where local differences will lead to a wider distribution in granule size distribution and properties in an unpredictable fashion. Fluid-bed processors can be one of the most uniform processes in terms of mixing and temperature. Powder frictional forces are overcome as drag forces of the fluidizing air support bed weight, and gas bubbles promote rapid and intensive mixing. With regard to bed weight, forces in fluid-beds and, therefore, consolidation and granule density, generally scale with bed height. In fluid-bed granulation, growth rate is largely controlled by spray rate and distribution and consolidation rate by bed height and peak bed moisture. Particle growth in a fluidized bed is closely related to the particle mixing and flow pattern in the bed. This dictates that the hydrodynamics of the scaled batch should be the same as the small unit. He et al. (126) suggested scaling rules for fluid-bed granulators. They are summarized as follows:

1. Maintain the fluidized bed height constant. Granule density and attrition rate increase with the operating bed height.
2. If the bed height is kept similar, then the scaling will be dependent on the cross-sectional area of the bed.
3. Maintain constant superficial gas velocity to keep excess gas velocity, and therefore bubbling and mixing conditions, similar.
4. Increase the area of the bed under the spray (spray flux) by increasing the number of nozzles. This will allow the spray rate to increase and result in similar process times.

The amount of fluidization gas required to maintain constant fluidization velocity scales linearly with the cross section of the bed. However, for large fluidized beds, one of the major concerns is the even distribution of the fluidization gas across the whole area of the bed. Thus redesign of the air distributor and lower plenum modification may be required.

Regulatory Perspective

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. In 1991, the American Association of Pharmaceutical Scientists (AAPS), together with the U.S. FDA held a workshop on scale-up (127) where several speakers presented scale-up issues from an industrial and regulatory perspective. For example, Shangraw divided scale-up problems in two general categories: those related to raw materials or formulation and those related to processing equipment. He also indicated that it is essential to ascertain whether or not changes in raw materials have occurred before one looks at processing/equipment

changes as a source of any problem. The workshop report as it pertains to the process and equipment is reproduced below.

"*It is generally recognized that many NDAs and ANDAs contain provision for multiple manufacturers of the drug substance(s), and that not all drug substance suppliers, a priori, produce equivalent material. There is then a need for material quality control to assure the performance and reproducibility of the finished product. Particle size and distribution, morphology, and intrinsic dissolution of the drug substance are important considerations. Polymorphism, hygroscopicity, surface area, wettability, density (bulk and tapped), compressibility (for dry blending), and powder flow effects should be controlled.*

Additionally, the process should be controlled by employment of a validation protocol, which defines the critical parameters and also establishes the acceptance criteria for the granulation or blend and which may include sieve analysis, flow, density, uniformity and compressibility, moisture content, etc.

In the milling, blending, granulating and or drying processes, the operating principles of the equipment employed should be defined, and the variables determined. The impact and mechanism of measurement on in-process variables should be defined. Time, temperature, work input of equipment, blend/granulation volume, and granulating rate should be determined.

The parameters selected should be appropriate for the process, in those cases where the manufacturing process has been controlled and validated as specified in the foregoing discussion, batch scale-up, changes in site of manufacture, allowance for equipment change (where the operating principle is the same), minor formulation changes, etc., should be determined on the basis of the comparability of both the blend/granulation and the final product as assured by: (1) appropriate tests, (2) specifications, (3) process validation, and (4) comparative accelerated stability".

In 1995, the FDA issued Scale-up and Post-Approval Changes (SUPAC) guidance for the industry (128) for immediate release dosage forms and in 1997, SUPAC–MR guidance was released for modified release dosage forms (129).

Scale-Up and Equipment Design

The scale-up from the laboratory equipment to production size units is dependent on equipment design which may or may not have been scalable as far as its dimensional feature or components selection is concerned. The importance of scalability is well understood and accepted by the manufacturers of fluid-bed processors. Various sizes in their product line are logically designated and manufactured. Airflow in the fluid-bed process is a critical parameter. The design and selection of the processor is very important for the laboratory and production unit. Because airflow is one of the components of the drying capacity of a fluid-bed system, ratio of air volume per kg or liter of the product is very critical to achieve scale-up that is linear.

The other design feature is the cross-sectional area of the product container, and how it has been designed throughout the various sizes that a manufacturer supplies. The relationship between various sizes of the process containers can be utilized to calculate the scale-up of binder spray rate and if the cross-sectional area is designed linearly, then the spray rate scale-up can be linear.

Process Control and Scale-Up

The fluid-bed agglomeration process is a combination of three steps, namely, dry mixing, spray agglomeration, and drying to a desired moisture level. These process steps are equally important. But the quality of the granules is really determined during the spraying stage, where constant building of granules and evaporation of binder solvent is taking place. Granule size is directly proportional to the bed humidity during granulation (47) and, hence, control of this humidity during scale-up is essential.

Gore et al. (130) studied the factors affecting the fluid-bed process during scale-up. The authors found that processing factors that most affected granule characteristics were process air temperature, height of the spray nozzle from the bed, rate of binder addition and the degree of atomization of the binder liquid.

The atomizing air pressure and the wetness of the bed are two of the most important elements of fluid-bed granulation. A higher atomizing air pressure yields a finer droplet of binder solution. Therefore, granule growth, as described earlier in this section, will be affected by the atomizing air pressure. A major factor which must be considered during the scale-up of fluid-bed granulation process is maintaining the same droplet size of the binder to assure successful scale-up. A recent study (131) confirmed the influence of spray nozzle set up parameters and drying capacity of the air. The study concluded that more attention should be paid to the easily overlooked nozzle atomizing air pressure and volume. When considering the atomizing air pressure, attention must be paid to ensure enough air is delivered to the nozzle tip. This can be assured by placing air pressure and volume measurement devices at the nozzle. The data also shows that the drying capacity of the process air influences the final granulated particle size. Jones (132) has suggested various process-related factors that should be considered during the scale-up of a fluid-bed processing.

Due to the higher degree of attrition in the larger unit compared to the smaller unit, the bulk density of the granulation from the larger fluid-bed is approximately 20% higher than the smaller unit. Jones also re-emphasized the importance of keeping the bed moisture level below critical moisture level to prevent the formation of larger agglomerates. Since the higher airflow along with the temperature (drying capacity) in a larger unit provide higher evaporation rate, one must maintain the drying capacity in the larger unit, such that the bed temperature is similar to the smaller unit bed

temperature. This can be accomplished either by increased spray rate, increased air temperature, increased airflow or the combination of these variables to obtain suitable results. Since the ratio of bed depth to the air distributor increases with the size of the equipment, the fluidization air velocity is kept constant by increasing the air volume.

In the past, the scale-up was carried out by selecting best guess process parameters. The recent trend is to employ the Factorial and Modified Factorial Designs and Search Methods. These statistically designed experimental plans can generate mathematical relationships between the independent variables, such as process factors, and dependent variables, such as product properties. This approach still requires an effective laboratory/pilot scale development program and an understanding of the variables that affect the product properties.

In summary, when scaling-up, the following processing conditions should be similar to the pilot scale studies:

1. fluidization velocity of the process air through the system
2. the ratio of granulation spray rate to drying capacity of fluidization air volume
3. droplet size of the binder spray liquid

Each of these values must be calculated based on the results of the operation of the pilot-size unit. Pilot-size equipment studies should also be conducted in a wide range to determine the allowable operating range for the process.

In the fluid-bed granulation process, moisture control is the key parameter that needs to be controlled. Faure et al. (133) have used process control for scale-up of a fluidized bed process. They used infra-red probes to monitor moisture. As there are normally large numbers of inter-related variables, they used computerized techniques for process control, such as fuzzy logic, neural networks, and models based on experimental techniques.

Rambali et al. (134) scaled-up fluid-bed process based on the relative droplet size and the powder bed moisture content at the end of the spraying cycle. They scaled-up from 5 to 30 kg and then to 120 kg. with a geometric mean granule size of 400 μm.

Some of the researchers have addressed scale-up problems by adopting the semi-continuous granulation techniques (135,136).

Werani et al. studied quasi-continuous scale-up of a fluid-bed drying after wet granulating in high shear mixer. By using series of fluid-beds (multi-cell units), they transferred wet granulated product to the first fluid-bed dryer; when that batch was semidried, it was transferred to the next fluid-bed unit in the series, while the first unit was loaded with freshly granulated batch. This continued until all the cells (fluid-bed units) were full and the discharge from the last unit provided a dried product, thus providing a quasi-continuous process (137).

CASE STUDY

The following case study illustrates how a product is scaled-up from 15 to 150 kg in equipment supplied by Niro pharma systems once one understands the critical process parameters used when scaling-up.

A spray granulation process was developed for a common pharmaceutical compound. The granulation process involved spraying of a 5% w/w binder solution onto the fluidized powder. Table 5 shows the data from the 15 kg run and resultant successful 150-kg run condition for a spray agglomeration process (138).

Airflow Calculations

To maintain the same fluidization velocity, the air volume in a larger unit must be increased, based upon the cross-sectional area of the product bowl. In this case, the cross-sectional area of the base of the larger container was 0.77 m^2 and the smaller was 0.06 m^2. The correct airflow should be calculated as $300 \times (0.77/0.06) = 3850$ CMH. This number was further modified after considering the increase in bed depth in a larger unit, to 4000 CMH.

Spray Rate Calculations

To maintain the same particle size the triple-headed nozzle could spray three times the pilot unit spray rate at a 2.5 atomization air pressure. However, this could result in a longer process time. Another approach to maintain the similar droplet size is to maintain the mass balance of spray rate and the atomization pressure. Thus, by increasing the atomization pressure to 5 bar, the spray rate was increased to 800 g/min, keeping the same droplet size and, hence, obtaining granulation with the desired characteristics.

Temperature Calculations

Finally, required inlet temperature was recalculated, based upon the change in ratio of air volume to spray rate. Because the air volume was increased

Table 5 Scale-Up Process Parameters from 15 kg to 150 kg Batch

Process parameters	15 kg	150 kg
Air flow [cubic meters per hour (CMH)]	300	4,000
Inlet air temperature (°C)	55	50
Spray rate (g/min)	100	800
Nozzle air pressure (bar)	2.5	5
Container cross-sectional area of the base (m^2)	0.06	0.77
Number of nozzles	1	3

over 13 times but the spray rate was only increased eight times, the inlet temperature was reduced to 50°C. This adjustment in drying capacity was necessary to avoid spray drying of the spray solution. (A three-headed nozzle used in this scale-up can be replaced by a six-headed nozzle. This would have resulted in the ability to increase the spraying rate 13 times above the pilot size unit to match the airflow. The maintenance of droplet size, and temperature could have been achieved with a six-headed nozzle. The end result would be reduced process time.) Figure 24 shows the particle size distribution produced using a 15 kg unit and a 150 kg unit.

MATERIAL HANDLING

The transfer of materials to and from the fluid-bed processor is an important consideration. The loading and unloading of the processing bowl can be accomplished by manual mode or by automated methods.

Loading

The contemporary method for loading the unit is by removing the product bowl from the unit, charging the material into the bowl, and then placing the bowl back into the unit. This loading is simple and cost effective. Unfortunately, it has the potential of exposing the operators to the product and contaminating the working area. To avoid the product becoming a dust and cleaning hazard, a dust collection system should be installed to collect the dust before it spreads. A manual process also depends on the batch size, the operator's physical ability to handle the material and the container, full of product. Furthermore, this can be time consuming, since the solvent must be added to the product container one solvent at a time. The loading process

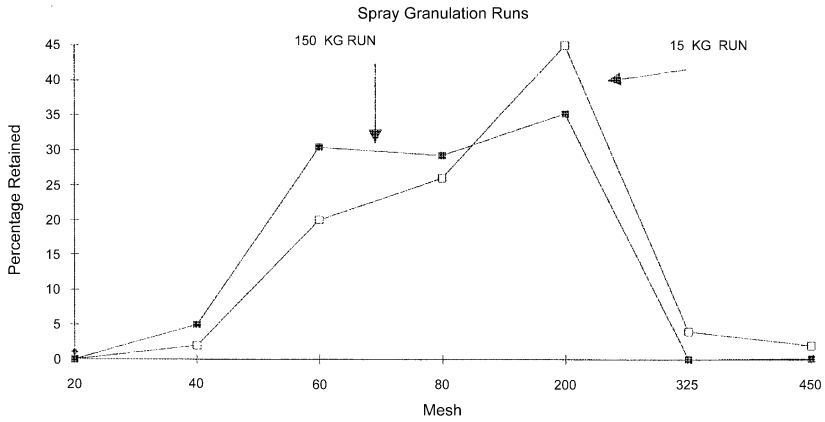

Figure 24 Scale-up case study and resultant particle size distribution.

can be automated and isolated to avoid worker exposure, minimize dust generation, and reduce loading time. There are two main type of loading systems. These systems are similar because both use the fluid-bed's capability to create a vacuum inside the unit. Here the product enters the fluid-bed through a product in-feed port on the side of the unit. This is done by having the fan running and the inlet air control flap set so that minimum airflow may pass through the product container and the outlet flap is almost fully open. Once the material has been charged to the fluid-bed, the product in-feed valve is closed and the granulating process started. This transfer method uses some amount of air to help the material move through the tube. Figure 25 shows the set up for loading of the fluid-bed. Loading can be done either vertically from a overhead bin or from the ground. Less air is required through the transfer pipe when the material is transferred vertically, because gravity is working to help the process. Vertical transfer methods do require greater available height in the process area. Loading by this method has the advantages of limited operator exposure to the product, allows the product to be fluidized as it enters the processor and reduces the loading time. The disadvantage of this type of system is the cleaning required between different products.

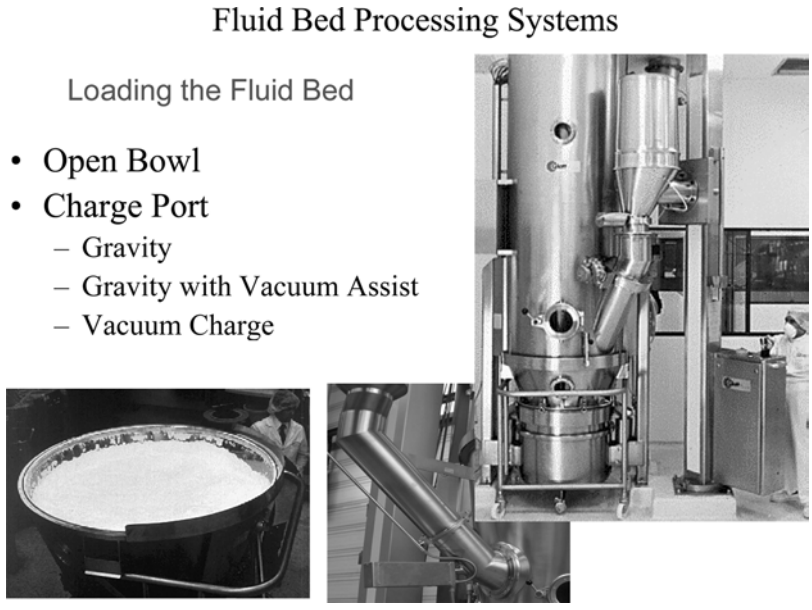

Figure 25 Various options for loading the fluid-bed. *Source*: Courtesy of the Glatt Group.

Unloading

As with loading, the standard method for unloading is by removing the product bowl from the unit. Once the bowl is removed, the operator may scoop the material from the bowl, which is the most time consuming and impractical method, because of its potential of exposure to the product. Alternatively, the product can be vacuum transferred to a secondary container or unloaded by placing the product bowl into a bowl dumping device as shown in Figure 26. This hydraulic device is installed in the processing area. The mobile product container of the fluid-bed processor is pushed under the cone of the bowl dumper and they are coupled together by engaging the toggle locks. Subsequently, the container is lifted hydraulicaliy, pivoted around the lifting column, and rotated 180° for discharging.

Use of the bowl dumping device or vacuum unloading device still requires that the product bowl be removed from the unit.

There are contained and automated methods for unloading the product while the product bowl is still in the fluid-bed processor. The product may either be unloaded out of the bottom of the product container or from the side. Until recently, the most common contained method was to unload the material from the bottom of the unit. This required the ceiling height to be high enough to accommodate it or the installation would become a multi-

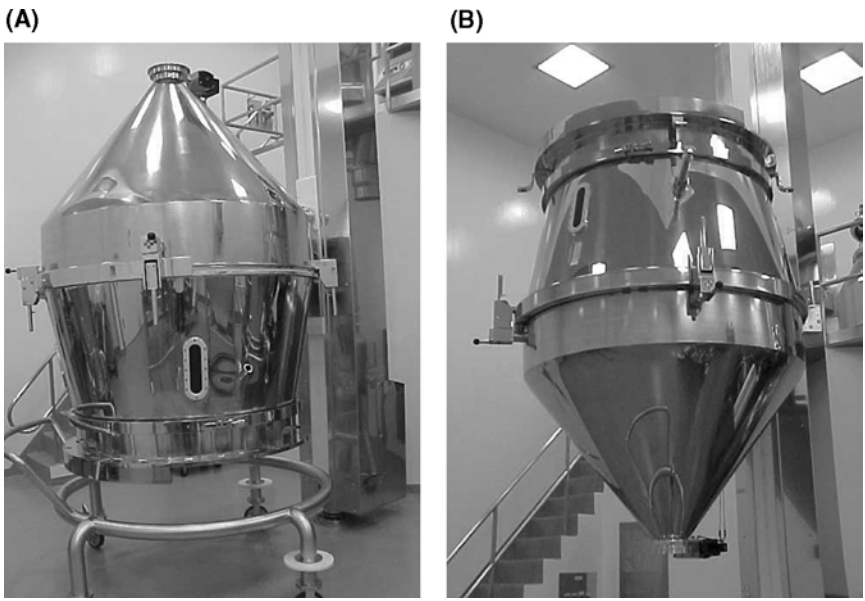

Figure 26 (**A**) and (**B**) Product discharge from the fluid-bed processing bowl using lift device. *Source*: Courtesy of Niro Pharma Systems.

storied installation. There are two types of bottom discharge options: gravity or pneumatic. Gravity discharge (Figs. 27 and 28) allows for collection of the product into the container that is located below the lower plenum. If the overall ceiling height limitation prevents discharge by gravity, the gravity/pneumatic transfer combination can be considered. The gravity discharge poses cleaning problems, since the process air and the product discharge follow the same path; assurance of cleanliness is always of prime concern.

The desire to limit the processing area and development of the overlap gill air distributor mentioned earlier in the chapter have prompted the consideration of side discharge as an option. The product bowl is fitted with the discharge gate, as shown in Figures 29 and 30. Most of the product, as it is free flowing granules, flows through the side discharge into a container. The remainder of the product is then discharged by manipulation of the

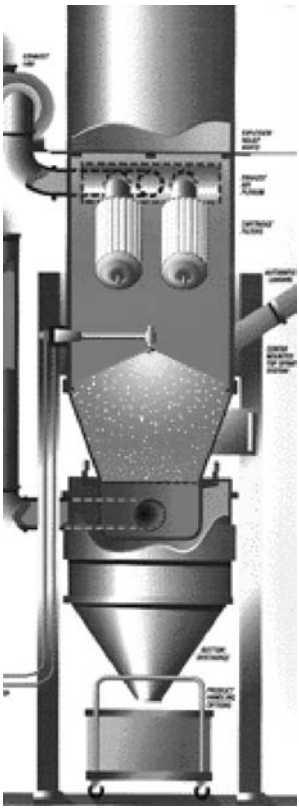

Figure 27 Product discharge from the bowl by gravity. *Source*: Courtesy of Vector Corporation.

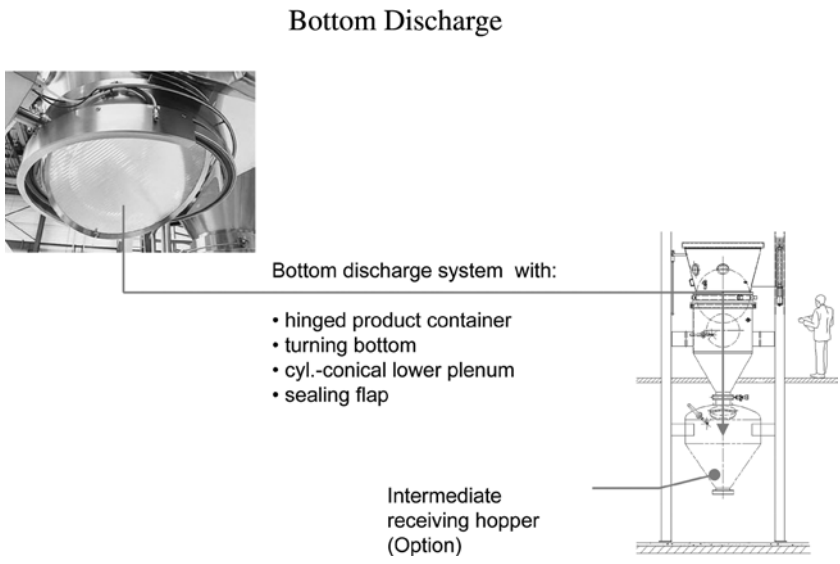

Figure 28 Product discharge from the bowl. *Source*: Courtesy of the Glatt Group.

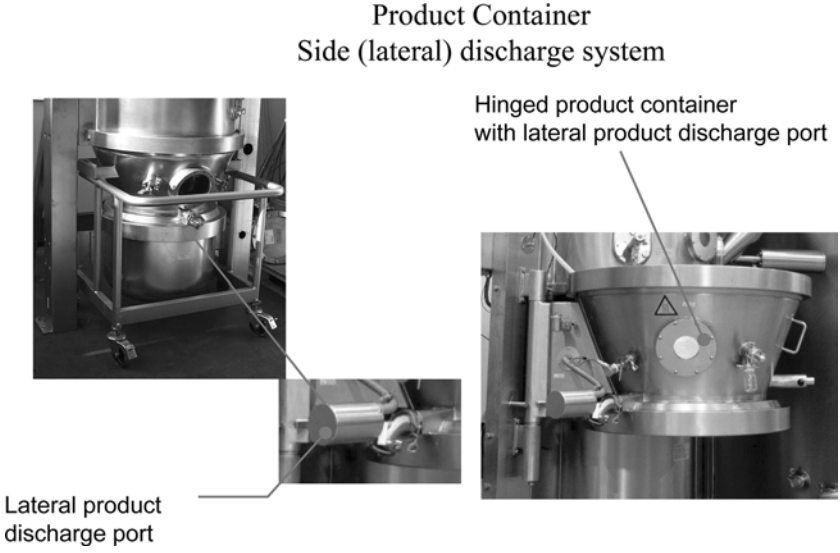

Figure 29 Side discharge from the product bowl. *Source*: Courtesy of the Glatt Group.

Figure 30 Side discharge from the product bowl. *Source*: Courtesy of Niro Pharma Systems.

air flow through the overlap gill air distributor. The discharged product can be pneumatically transported, to an overhead bin if dry milling of the granulation is desired.

The contained system for unloading the product helps to isolate the operator from the product. The isolation feature also prevents the product from being contaminated by being exposed to the working environment. Material handling considerations must be thought of early in the equipment procurement process. Fluid-bed processing, whether used as a integral part of high-shear mixer/fluid-bed dryer or as a granulating equipment option, production efficiency, and eventual automation can be enhanced by considering these loading and unloading options. A typical installation, with the loading and unloading of the fluid-bed from the high-shear mixer and intermediate bulk containers (IBC), is shown in Figures 31 and 32.

SUMMARY

Scale-up is normally identified with an incremental increase in batch size until a desired level of production is obtained. The fluid-bed process, similar to other granulation techniques, requires an understanding of the importance of characterization of the raw materials, especially of an active

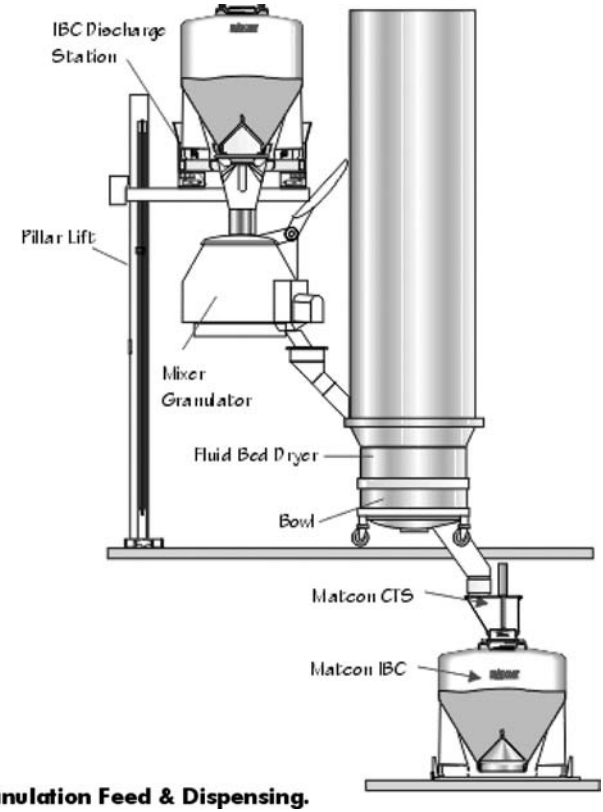

Figure 31 Schematic of product loading and unloading to and from the FB processor. *Source*: Courtesy of Matcon, U.S.A.

pharmaceutical ingredient, process equipment, limitations of the selected process, establishment of in-process control specifications, characterization of the finished product, and cleaning and process validation. It is equally important that the formulation and development scientists do not lose sight of the fact that the process being developed in the pilot plant will someday be transferred to the production floor. The scientists should spend enough time in the production department to understand the scale of operation for which the desired process is being developed. If the process development scientist has not spend enough time understanding the various interrelated variables, then it will be difficult to have a robust process for the commercial operation.

Scaling-up by maintaining the droplet size of the granulating liquid will enhance the probability of an uniform nucleation stage to build the granules.

Figure 32 Industrial installation of product loading and unloading to and from the FB processor. *Source*: Courtesy of Matcon, U.S.A.

Similarly, the scientist must think through how the material will be added and taken away from the processor on a commercial scale. Without this forethought, I have seen many times processes that come to production which are very labor intensive. If the development scientists work with production and engineering departments from an early stage, these difficulties can be avoided.

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11

Scale-Up of Extrusion and Spheronization

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INTRODUCTION

Extrusion-spheronization is a pelletization process for making pellets that are amenable for immediate and controlled-release preparations. It includes the processes of blending, granulation, extrusion, spheronization, drying, screening, functional coating (if needed), and encapsulation or compression into tablets. The major advantages in formulating drugs as pellets include (1) a high drug loading, improved homogeneity from uniform distribution of ingredients and improved wetting/dissolution due to a larger surface area than a single unit, such as a tablet. From a bioavailability standpoint, pellets minimize inter- and intrasubject variability and food effects as they undergo gradual but continuous and uniform gastric emptying. In addition, pellets are less prone to dose dumping that is commonly associated with a single unit, such as a tablet. Other advantages include improved flow properties, dust control, and marketing appeal. A list of marketed pellet dosage forms is shown in Table 1.

Although many types of pellet dosage forms have been introduced in the marketplace, a greater understanding is needed of the role of excipients, equipment, process variables, and controls involved in the pelletization process and those that govern successful scale-up from laboratory to

Table 1 Examples of Multilithic Drug Products (Pellets, Spheroids, Granules)

Brand name	Drug	Company	Product form	Market form
Xenical®	Orlistat	Roche	Uncoated pellets	Capsule
Nexium®	Esomeprazole Mg	Astrazenaca LP	Delayed release pellets	Capsule
Toprol-XL®	Metoprolol succinate	Astrazeneca LP	EXR Coated pellets	Tablet
Verelan PM®	Verapamil HCl	Schwarz	EXR Pellets with controlled onset	Capsule
Singulair®	Montelukast sodium	Merck	Oral granules	Granule
Prevpac® *& Prevacid*®	Lansoprazole	TAP	Enteric granules	Capsule
Paser®	Aminosalicylic Acid	Jacobus	Enteric granules	Granule
Effexor XR®	Venlafaxine	Wyeth	EXR Spheroids	Capsule
Aggrenox®	Aspirin IR Dipyrimadole ER	Bohringer Ingelheim	EXR Pellets + Tablets	Capsule
Cymbalta®	Duloxetine	Eli Lilly	EXR Pellets	Capsule
Dexedrine® *Spansule*®	Dextroamphetamine	GSK	SR Pellets	Capsule

Source: PDR Electronic Library, 2005, Main Edition.

manufacturing. The following chapter describes critical aspects in the scale-up of the extrusion-spheronization process, including the influence of equipment, excipients, process conditions, and controls. Finally, some aspects related to monitoring extrusion-spheronization under the FDA's Process Analytical Technologies (PAT) initiative using on-line process controls are also presented.

EXTRUSION-SPHERONIZATION—AN OVERVIEW

Newitt and Conway-Jones defined (2) pelletization as the process of transforming a wet, solid mass of finely divided particles into dry, spherical bodies by a continuous rolling or tumbling motion. In a broader sense, pelletization is an agglomeration event used in many powder processes, either for ease of handling or to add value to the product. It spans a range of industries that process solid particles into some suitable form, such as metallurgical, chemical, plastics, fertilizer, rubber, food, and pharmaceuticals (3–6). Since spheres have the lowest surface to volume ratio and exhibit

reproducible packing, an ideal pelletizing process should produce spheroids with the required tensile strength, density, uniformity of content, size, and a narrow size distribution. In addition, for the pharmaceutical industry, such processes must meet its unique needs of safety, quality, potency, bioavailability, and regulatory conformance.

Webster (7) defines extrusion (*ex* + *trudere*) as an act to expel, thrust, force or push out material, i.e., to shape by forcing through dies under pressure. In other words, extrusion is a molding or shaping process in which an irregular, shapeless mass of wet or molten material is molded into a regular, three-dimensional, solid object with a measurable size, shape, and content. The extruded product is often subject to a further shaping and sizing process to obtain spherical pellets by the process of spheronization (also referred to as spheroidization), first invented (and patented) in Japan by Nakahara (8) in 1966. It describes a method of preparing spherical granules from a wet powder mixture. It became widely known in the United States in the 1970s after it was introduced by Conine and Hadley of Eli Lilly & Co. (9,10). It is also referred to as "marumerization" after the trade mark of the Fuji Denki Kogyo company in Japan.

Extrusion-spheronization is a technique for making spherical pellets, the oldest of which is the art of pill-making (9). Traditional pill-making and extrusion-spheronization begin with a wet massing stage, common to both, in which medicaments and excipients are mixed with suitable binders to form a plastic mass. The difference between the two is that in pill-making, the wet mass is rolled into cylinders which are then cut and rolled into spherical balls manually. In spheronization, the wet mass is extruded into cylinders which are then shaped into spherical pellets in a spheronizer. It is therefore regarded as a fast, efficient, and novel pill-making process. Melt extrusion is a variant of wet extrusion in which, instead of a wet mass, a molten mass is extruded.

Extrusion-spheronization can provide highly dense, spherical pellets with a smooth surface and a narrow particle size distribution and with drug loading as high as 90%. It is also amenable to batch or continuous processing (9–11). A schematic of extrusion-spheronization and associated unit operations (12,13) are shown in Figure 1.

A typical process begins with a dry blend of drug and excipient that is suitably wetted with water, a water-solvent mixture or a binder solution to form a wet agglomerated mass. The wet mass is conveyed by one or more feeder screws in a suitable configuration and forced through a perforated screen or die, resulting in a short, right cylindrical, or rod-shaped extrudate. The extrudates are rotated at a suitable speed over a friction plate in a spheronizer (Marumerizer®). The rods are broken down into cylindrical pieces of uniform length and rolled into spheres by frictional, centrifugal, and centripetal forces during rotation in the spheronizer within 30 seconds to several minutes, depending on the formulation attributes. A diagrammatic

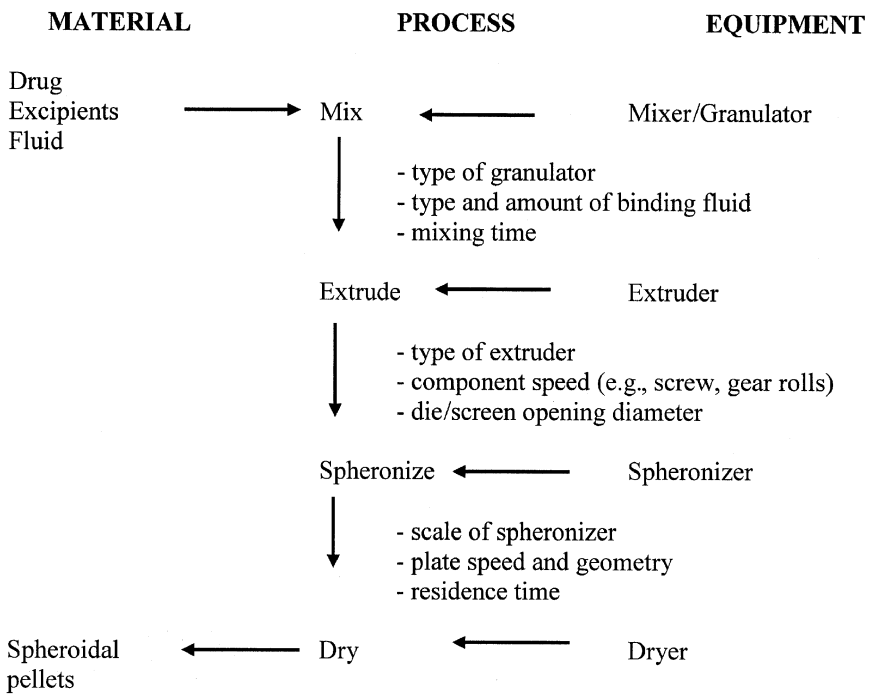

Figure 1 A schematic of the extrusion-spheronization process and associated unit operations.

sketch of the process is shown in Figure 2. The key variables for successful development of the extrusion-spheronization process are:

- formulation (selection of excipients),
- wet granulation (particularly moisture content),
- extruder design and extrusion parameters, and
- spheronizer design and spheronization parameters.

For the sake of clarity, the formulation and granulation aspects are in tandem as they relate to the extrusion and spheronizationprocesses rather than discussed separately.

EXTRUSION

The attributes of the extrudate, such as density, thickness, and moisture content, are controlled by variables due to the formulation, extrusion process, and equipment design. The properties of the wet feed material and its ability

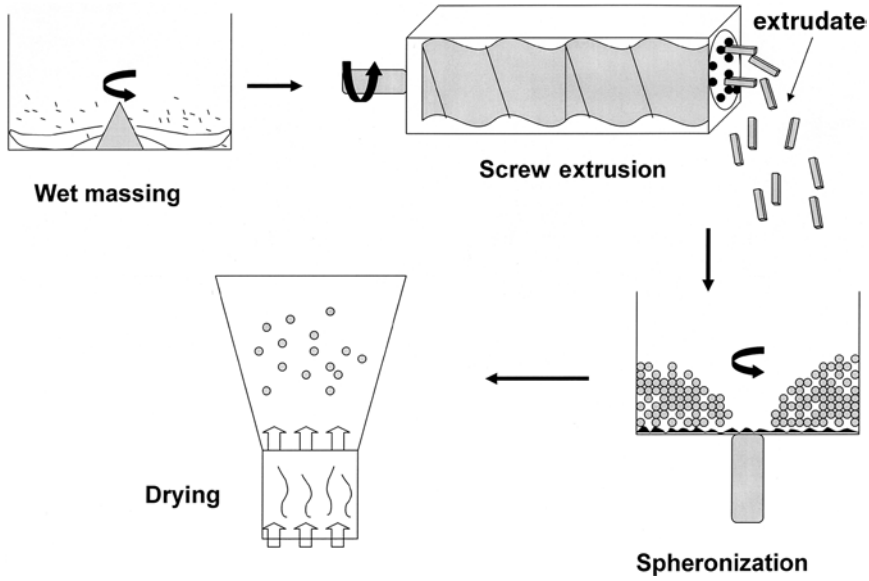

Figure 2 A diagram of the critical operations in extrusion-spheronization.

to extrude under pressure, feed rate, design of extruder components such as screen and screw elements are critical considerations in extrusion. While the moisture content of the wet mass determines its binding and lubrication during transport, the mechanical variables largely influence temperature, shear stress and throughput rates in extrusion. The various aspects related to scale-up of extrusion process ranging from equipment design to in-process controls and formulation considerations are discussed in the following sections.

Equipment Design

Extruders can be broadly classified (14,15) as screw and cylinder extruders, based on the feed mechanism that transports the wet mass towards the die and further based on the die configuration and discharge mechanisms. Figure 3 shows extruders of varying scales from lab to production while Figure 4 shows schematics of the various configurations of extruders used in the pharmaceutical industry. A comparison of attributes of various types of extruders is shown in Table 2.

Screw Feed Extruders

The screw extruder is a hollow chamber of suitable length that contains single or double rotating screws driven by a variable speed drive to transport

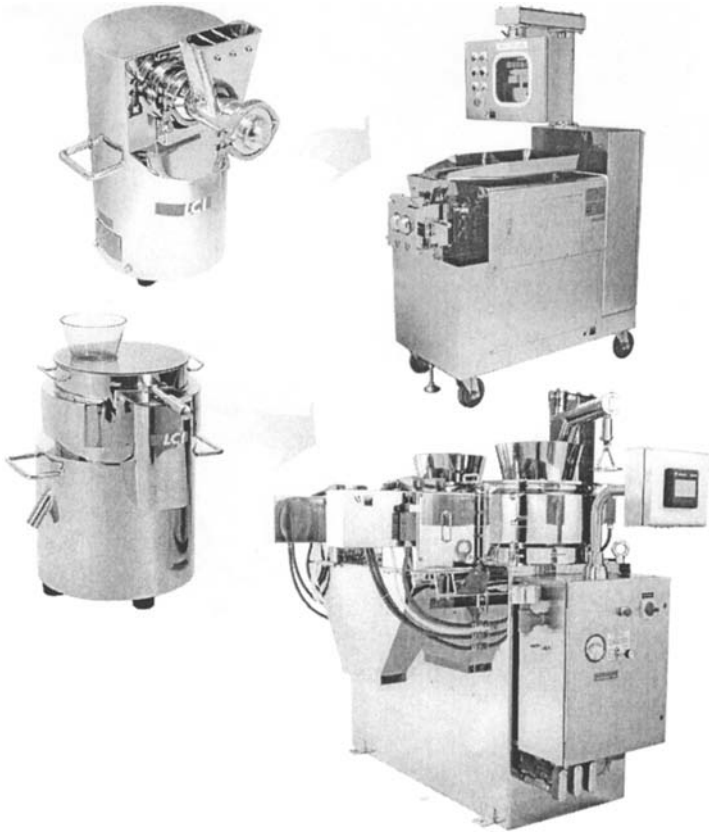

Figure 3 Extruders and spheronizers, lab scale to production. *Source*: Courtesy of LCI.

the wet mass through the cylinder. The wet mass is fed into the void space at the up-stream end of the drive, transported through the cylinder and pushed through a perforated screen or die. Some shear work is required in screw extruders to generate the pressure needed for extrusion, leading to a rise in temperature in the chamber. A cooling jacket around the chamber is an option to offset the heat buildup. The double-screw type has either co- or counter-rotating screws. The LCI and Gabler extruders belong to this class. Based on the orientation of the feed screw and discharge mechanism, extruders can be further classified as:

1. Axial feed/Axial discharge (A–A).
2. Horizontal feed/Radial discharge (A–R).
3. Vertical feed (gravity)/Radial discharge (R–R).

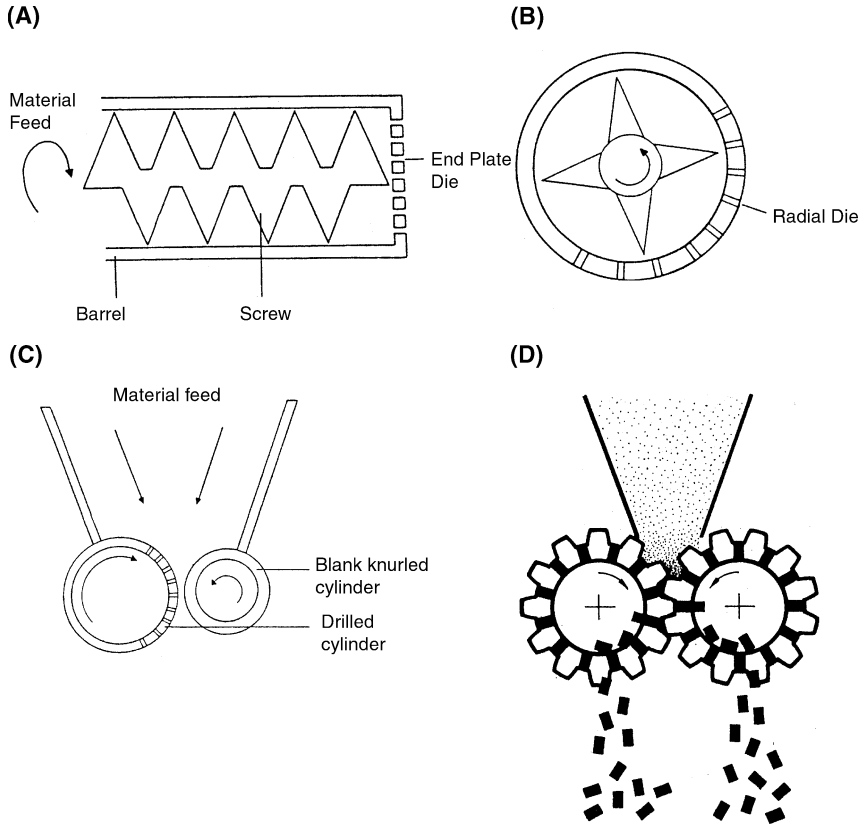

Figure 4 Schematics of the various configurations of extruders used in the pharmaceutical industry.

The A–A extruders are equipped with a flat perforated plate or screen, combined with two flat extrusion heads. The wet mass is pressed axially through the screen parallel to the feed screws. The extrusion forces are the highest, compared to other low pressure extruders, resulting in a hard and dense extrudate. It is commonly used in the extrusion of food, thermoplastics, and other industries, where a large pellet diameter and thermosetting properties are desired.

In the A–R type, the feed screws end in blades that rotate along the horizontal axis but force the wet mass through a screen-placed radial or cylindrical around the blades (Fig. 5). The A–R extruders have somewhat conical extrusion heads resulting in an "overflow," i.e., a certain amount of feed material is pushed axially between the screen and extrusion head at the front instead of radially through the screen area. A greater open area of screen results in a higher and faster throughput. However, the hardness

Table 2 A Comparison of Attributes of Different Types of Extruders Based on Feed and Discharge Geometries

	A–A	A–R	A–A (dome)	R–R (basket)	Gear/cylinder	Roller
Feed	Axial	Axial (horiz.)	Axial	Axial (gravity)	Axial (gravity)	Axial (gravity)
Discharge	Axial	Radial	Axial	Radial	Gear–axial cylinder-radial	Radial
Screw/roll configuration	Single or twin	Single or twin	Single or twin	Single	Dual roothed gears/dual cylinders (one blank and one drilled)	Dual solid
Screen configuration	Flat screen/ die with flat extrusion heads	Radial screen with conical extrusion heads	Hemispherical screen with dome shaped extrusion heads	Vertical screw with two or more extrusion blades	No screen; Extrudate size based on size of drilled holes	Radial screen with roller extrusion heads
Typical extrudate	Hard and highly dense	Medium	Medium	Soft and poorly dense	Medium	
Throughput	Low	Low	Medium	High	Medium	Medium
Energy use	++++	+++	++	+	+	+
Temperature	Up to 100°C	Up to 60°C	Up to 40°C	Up to 10°C	10–20°C	10–20°C
Screen opening	2–15 mm	0.5–3 mm	0.3–2 mm	0.5–2 mm		
Scale-up	Based on L/D ratio	Need to adjust water level	Some adjustment of water level may be needed	Straightforward	Straightforward	Some adjustment of water level needed

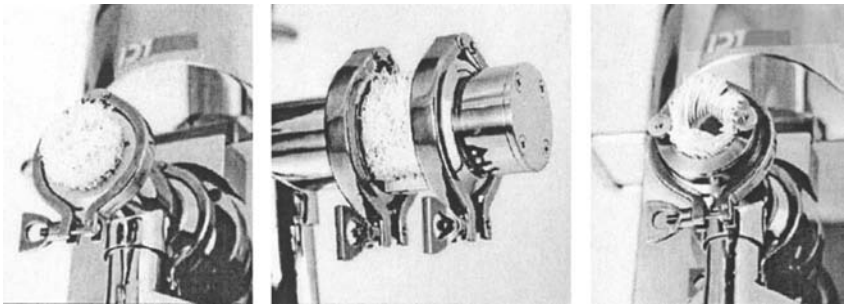

Figure 5 Axial, radial and dome extrusion assembly. *Source*: Courtesy of LCI.

and density of the resulting extrudate are lower than in A–A extruders, due to the lower force of extrusion.

The dome extruder is a variation of the radial extruder that uses a dome-shaped (hemispherical) screen in combination with dome-shaped extrusion heads, introduced by Fuji Paudal, Inc. in 1992 as the TDG series. This generates lower pressure than the axial and radial extruders, resulting in extrudate with lower density and hardness. The dome extruder has almost no ''overflow,'' resulting in higher throughput.

The R–R type, also known as a basket extruder, consists of a vertical rotating shaft with two or four extrusion blades located inside a right cylindrical screen and moving along the major axis of the cylinder. The material is fed by gravity from a hopper located above the cylindrical screen while the rotating blades press the material through the screen openings. The wet mass is not under pressure except during the actual extrusion. The low heat buildup makes it amenable for thermally unstable formulations. An example of a basket extruder is shown in Figure 6. The NICA and LCI BR extruders belong to this class.

Cylinder Extruders

In these extruders, the wet mass is fed into the nip formed between two cylinders, which are either rollers or a set of hollow, toothed meshing gear wheels as shown in Figure 7. In the former, the dies are in the form of a perforated cylinder, while in the latter, they are in the form of holes drilled between the gear teeth down to the hollow bore. In both cases, the extrudate exits from the center of the arrangement (16). A shear stress is generated only on the wet mass held either in the nip between the cylinders (rolls) or that flows through the die land (gear) instead of on the entire mass as in screw extruders. The advantages of low shear and minimal heat buildup may be offset by low throughput as the heavy gears rotate at a slow speed (<50 rpm). The Caleva and Alexanderwerk extruders belong to this class.

Figure 6 An example of extrusion through a basket extruder. *Source*: Courtesy of LCI.

Table 3 provides an overview of extruders of varying scales and capacities available in the marketplace.

Process Control and Scale-Up

Dimensional Analysis in Scale-Up of Extrusion

Dimensional analysis is a tool often used to express similarities between two scales, both geometric and dynamic. It has been applied to distributive mixing and conveying processes in compounding extruders (17–21) where the screw is segmented and composed of feed, mixing, and shearing elements, unlike wet extrusion that typically employs a single pitch, non-segmented screw element. However, since extrusion is similar in both cases, an example of such an analysis from melt extrusion literature is presented here.

In its simplest form, the ratio of screw diameter is the basis for scaling. The ratio of the large diameter D_2 of the large scale unit to the small diameter D_1 of the lab unit is represented by the lower case d as shown in Table 4. The primary scaling variables are channel depth H, screw length L, helix angle ϕ, and screw speed N. The ratio of the primary variables of the two scales is then expressed as a power of the screw diameter ratio, d.

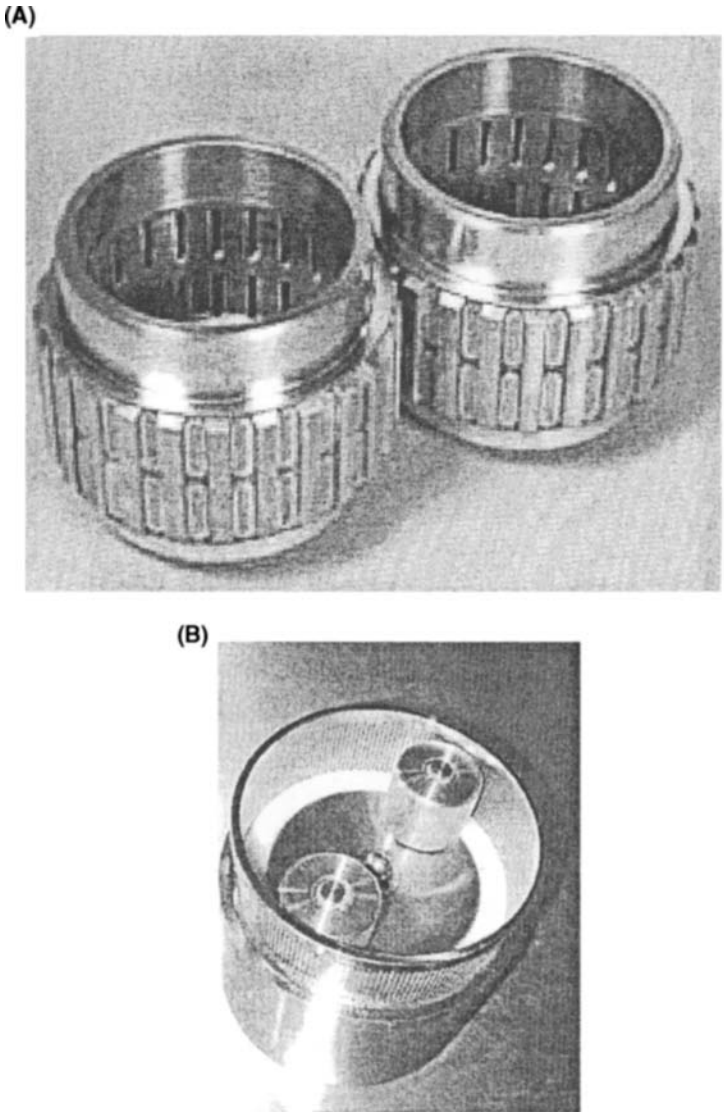

Figure 7 Cylinder extruder parts: (**A**) extrusion gears, (**B**) extrusion rollers. *Source*: Courtesy of Caleva.

The secondary variables, such as shear rate, mean residence time, power consumption, throughput rate, etc., are expressed as a function of the primary variables. For example, the shear rate (or material displacement rate) in the screw channel is a function of the primary variables D, N, and H

Table 3 An Overview of Extruders of Varying Scales and Capacities

Configuration	Model	Capacity (kg/hr)	Speed (rpm)
	LCI		
Axial	EXDF-60	50–100	
	EXDF-100	150–200	
	EXDF-130	300–400	
	EXDF-180	500–800	
Radial[a] (twin-screw)	EXD-60	30–50	19–75
	EXD-100	50–200	20–85
	EXD-130	200–500	20–85
	EXD-180	500–1200	
Dome[a]	TDG-80	100–150	30–120
	TDG-110	200–300	40–160
	TDG-220	800–1200	
Basket[b]	BR-150		10–90
	BR-200G	50–100	12–50
	BR-300G	100–300	12–50
	BR-450G	150–750	12–50
	Caleva		
Radial screw	Extruder 20	~25 kg	
Cylinder roller	Extruder 35	200	
Gear	Extruder 40C M	40–100	
	Extruder 40C A	40–100	
	Extruder 100	Upto 200	25–130
	Alexanderwerk		
Gear	GA-65 Granulator	30–50	
Basket 0.5–10 mm	RFG 150D	600	
	RFG 250D	1500	
	RFG 250DL	3000	
	RFG 250DDL	4500	
	NICA		
Basket	E140	30–120	
	E200	120–480	
	Gabler		
Axial	DE-40	0.5–100	
	DE-60	5–200	
	DE-80	25–500	
	DE-120	100–1500	

[a]model number refers to distance from midpoint of right screw to midpoint of left screw (mm).
[b]model number refers to basket diameter (mm).

and proportional to $1 + v - h$, a scale-up factor. For a given type of screw with fixed helix angle ($b = 0$), at fixed speed, N and fixed L/D and H/D ratios, the shear rate is constant as $1 + v - h = 0$ while, at varying screw speeds across scale, the total shear S remains constant.

Table 4 Geometric Scaling Ratios of Primary and Secondary Variables for Screw Extruder

	Small unit	Large unit	Cube rule N–constant D/H-constant	Square-root rule $H \sim \sqrt{d}$ $N \sim 1/\sqrt{d}$
Primary variables				
Screw diameter (D, m)	D_1	$D_2 = D_1 d$		
Channel depth (H, m)	H_1	$H_2 = H_1 d^h$	$h = 1$	$h = 0.5$
Screw length (L, m)	L_1	$L_2 = L_1 d^l$		
Helix angle (ϕ, radians)	ϕ_1	$\phi_2 = \phi_1 d^b$		
Screw speed (N, rpm)	N_1	$N_2 = N_1 d^{\nu}$	$\nu = 0$	$\nu = -0.5$
Secondary variables				
Shear rate (γ)	γ_1	γ_2	$\gamma_1 = \gamma_2 = \frac{\pi.D.N}{H}$	$\gamma_2 = \gamma_1.d$
Mean residence time (T, sec)	T_1	T_2	$T_1 = T_2 = \frac{L}{\pi.N.D.\mathrm{Sin}\phi}$	
Power consumption (E, watt)	E_1	E_2	$E_2 = E_1.d^3$	$E_2 = E_1.d^{2.5}$
Throughput rate (Q, kg/h)	Q_1	Q_2	$Q_2 = Q_1.d^3$	$Q_2 = Q_1.d^2$
Total shear (S) = f(γ_t, t)		S	$S = \frac{L}{H.\mathrm{Sin}\phi}$	

A constant total shear S suggests that the profiles of the material in the two different size screw extruders are identical or that the material distribution (homogeneity) in the extruder is independent of screw speed. In a similar manner, scale-up factors for power consumption, specific energy consumption, throughput rate, etc. have been compiled in the literature (21,22).

The scale-up factors depend on the specific event being scaled-up in extrusion. The "cube rule" for *mixing* (23) states that at constant screw speed, output and power consumption increase with d^3 when H/D ratio is constant. The "square-root rule" for conveying (24) of material states that when channel depth is increased and screw speed decreased with $\sqrt{d}$, the output rate increases with d^2, while power consumption increases by $d^{2.5}$. One could obtain scale-up factors (exponents) in a manner similar to the foregoing analysis in order to determine and monitor the secondary variables during scale-up.

The concept of similarities helps the reader in realizing the design attributes of extruders from smaller to larger scales for handling small to

large amounts of material. However, the process still needs to be monitored at each scale, using suitable criteria that are accurately and reproducibly measurable.

Process Monitoring

The goal in wet extrusion is to obtain a dense extrudate with a smooth surface and a thickness close to the diameter of the die or screen opening but also fragile enough to be broken down into short rods with an aspect ratio typically between 1 and 2. This is governed by the choice of formulation, process and equipment design variables shown in Table 5. In a typical scale-up operation, the formulation is provided by pharmaceutical R&D, while the equipment manufacturer provides the geometry and performance indicators, such as motor power consumption. The scale-up personnel therefore have to rely on the process variables and their control to monitor product performance. The early process parameters are often derived on small lab scale instruments with about 1 kg batch size, thus limiting their utility. However, critical parameters, such as moisture content of extrudate or process temperature, could still be measured at the smaller scale. Therefore, the ability to monitor the process critical parameters, should be considered during scale-up in addition to selection of the extruders and down-stream processing.

Table 5 An Overview of Formulation, Process, and Equipment Design Variables that Influence Extrudate Attributes

Formulation	Process	Geometry
Dry ingredients (drug, binder, filler)	Mixing	Extruder
particle size	Mixer speed (rpm)	Screw length, pitch and diameter
Solubility	Mixing time (min)	Screw channel depth
Crystallinity	Extrusion	Screw blade configuration
Melting point (°C)	Screw speed (rpm)	Die or screen configuration (radial, axial)
Thermal stability	Screen size (mm)	# of screws (single/dual)
Hygroscopicity	Feeding rate (g/min)	Die L/D ratio
Percent content	Spheronization	Roll diameter (mm)
	Plate speed (rpm)	Screw speed (rpm)
Wetting fluid	Residence time (min)	Spheronizer
Percent content	Material load (g)	Plate diameter (mm)
Dielectric	Drying	Groove distance (mm)
Viscosity (m.Pa.s)	Drying time (min)	Groove pattern
	Temperature (°C)	
	Type of dryer	

Evaluation of extrusion-spheronization for drug product manufacturing has focused on two main areas:

- mechanistic and kinetic aspects of the process using instrumented equipment,
- the impact of various formulation, process and device geometry variables on the physicomechanical properties of and drug release from dried pellets.

Instrumented extruders could be used to monitor continuously changing product attributes during extrusion. An instrumented extruder is equipped with transducers that measure the forces (or stress) developed during extrusion, which, in turn, is dependent on material properties and equipment geometry. This may be expressed as the pressure exerted by the blades or rolls at the screen or die during product exit (25), torque exerted on the screw shaft (26), shear stress in the barrel during material transport (27,28) and product temperature during exit at the screen or the die (26). These, in turn, are a function of the moisture (fluid), heat flow and shear rate gradients that develop during extrusion and impact the yield and properties of extrudate.

A common indicator in an extruder console is the power, E, consumed by the motor drive in transporting material from feed to product exit. A higher power consumption could mean greater friction during product movement or an overloaded chamber. The torque of extrusion (F) is the energy expended by the motor drive in rotating the screw(s) and is expressed as

$$F = E/N \tag{1}$$

where E is the power consumption to drive the screw shaft at a speed of N rpm.

Another indirect parameter is the specific energy consumption, K (29,30), which is the power normalized for throughput Q and expressed as

$$K = E/Q \tag{2}$$

$$K = (FN)/Q \tag{3}$$

Figure 8 shows the effect of speed on K at varying throughput rates. The value of K is similar when scaling from small (ZSK-30) to large (ZSK-53) extruders as long as the throughput rate is same across the scale. A question arises whether the specific energy should remain constant across scale. While K is a measure of energy expended in bonding and densifying the extrudate, it also is a measure of manufacturing efficiency as it relates to throughput rate.

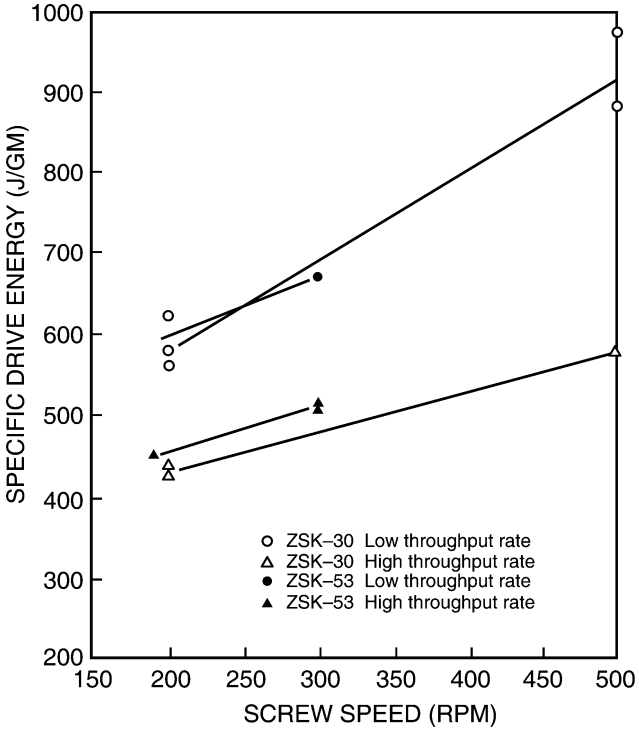

Figure 8 The effect of screw speed on specific energy consumption at varying throughput rates for extruders of two different scales. *Source*: From Ref. 29.

The torque, screen force, specific energy and power could be regarded as end-point metrics and, therefore, a measure of process conformance and product quality. Additional examples are shown in Table 6.

Selection of Extruders for Pharmaceuticals

Given that extruders of various designs, types and geometries are available in the marketplace, let us examine some aspects that drive selection of the appropriate extruder for a product. The key factors relevant in selecting the extruders are formulation factors (selection of excipients, thermal stability, plasticity, aqueous solubility, and moisture holding capacity) and equipment factors (batch versus continuous operation and scalability of the extruder).

Harrison et al. (27,31) obtained force-displacement profile during extrusion of microcrystalline cellulose (MCC) only formulations using a ram extruder and resolved it into three stages, as seen in Figure 9: compression, steady state, and forced flow. Based on surface smoothness and cohesive strength, a predominant steady state region was found necessary

Table 6 Examples of End-point Metrics for Product* and Process in Extrusion-Spheronization

Product	Process
Moisture content	Mixer output (e.g., torque of mixing, amperage, power consumption)
Particle size and size distribution	Torque or pressure of extrusion
Deformation behavior (e.g., strain, viscosity)	Barrel/die temperature
Shape and shape factors	Rate of evaporation (e.g., moisture, alcohol)
Density (e.g., bulk, tapped & true)	Shear rate of extrusion
Cohesive strength (e.g., tensile, compressive)	Throughput rate
Surface morphology (e.g., smoothness)	Extruder power consumption
Friability	Residence time
Porosity (volume and distribution)	Spheronizing torus volume
Drug release/dissolution rate	Plate angular velocity

*wet agglomerates, wet extrudate, or dried pellets.

for high-quality extrudate, while poor quality extrudate remained in the compression stage. The ejection stress based on angle of convergence from barrel to the die affects the surface smoothness of the extrudate and was found to be dependent on the moisture content.

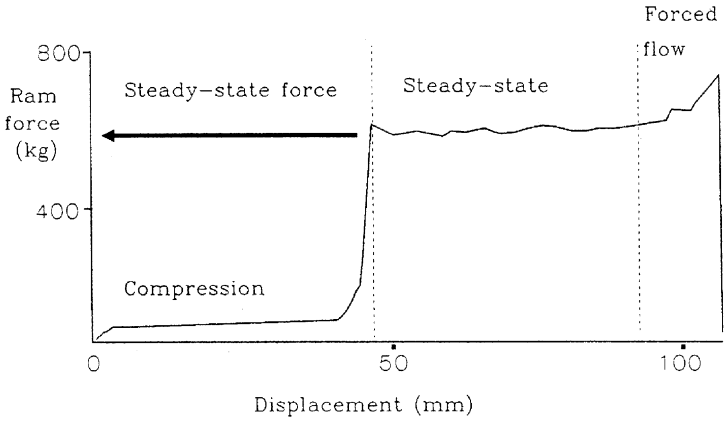

Figure 9 Schematic of a force-displacement profile from an instrumented ram extruder. *Source*: From Ref. 27.

The *ram extruder* develops high moisture and thermal gradients due to a high pressure build-up within the barrel. The product is axially compressed through a narrow die, resulting in temperatures as high as 150°C, which could be unsuitable for thermally unstable compounds. Although the ram extruder is more easily scaled up than other types of extruders, based on constant L/D ratio (L-barrel length, D-die diameter), it is not very amenable to continuous processing.

The *gravity* (*basket*) feed and screw extruders enable extrusion at relatively low-shear stress than in a ram extruder due to the following attributes:

- larger open area of screen or die lowers the extrusion pressure at exit
- lower shear within extrusion chamber due to lower effective contact area between screw surface and chamber wall.

The pressure exerted by the rotating extrusion heads on the screen as product is being pushed out in an A–R screw extruder (25) is shown in Figure 10. Each spike in the profile represents one revolution of the extrusion head while the frequency represents screw speed. Based on the shear stress developed during extrusion, wet mixtures of MCC-lactose had a lower yield stress in the radial screw extruder (130 kN/m^{-2}) than in the ram

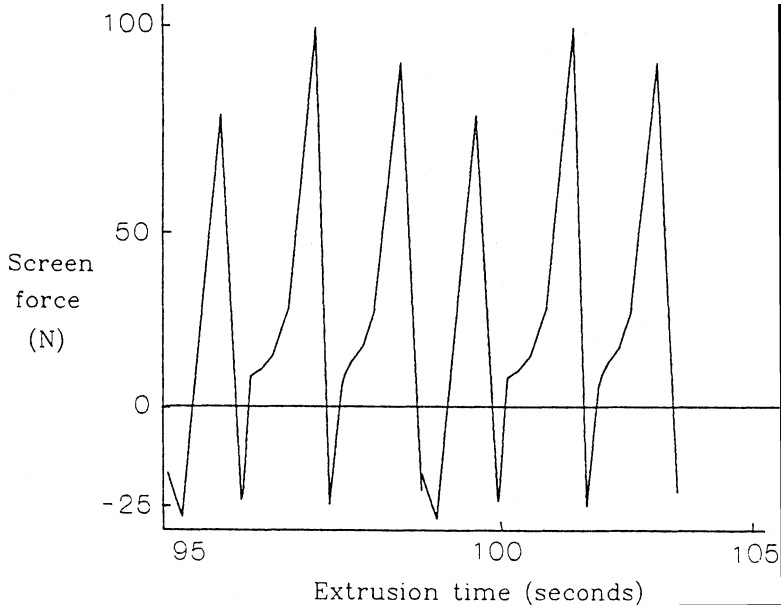

Figure 10 Schematic of a screen force profile from an instrumented radial screen screw extruder. *Source*: From Ref. 25.

extruder ($250\,kN/m^{-2}$), suggesting better performance of the cylinder extruder (32). Similarly, the basket and gravity feed roll (gear) extruders generate lower extrusion forces than axial screw extruders in which frictional forces are higher (28).

Among the formulation variables that control extrudability of a product, several studies (25,26,33–35) point to the fluid or moisture content of the wet feed material being more critical than others. The force or torque of extrusion and power consumption are often inversely proportional to moisture content of the extrudate as seen from Figures 11 and 12 (26,36–38), while the particle size of pellets increases linearly with water content when extruded with gravity feed basket and roll extruders (33). Using instrumented gravity feed and radial screw extruders, a three- to fourfold decrease in the force has been noted, with a 10% increase in water content of feed material (37).

The aqueous solubility of solid ingredients is inversely proportional to the water content required to obtain acceptable pellets (39), as shown in

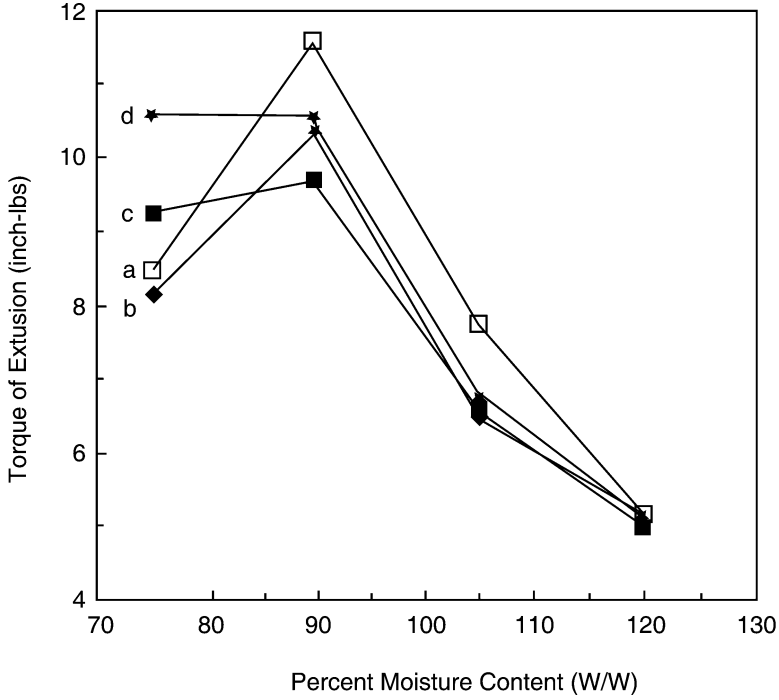

Figure 11 Torque of extrusion as a function of moisture content of wet mass of MCC at varying screw speeds: *a*-19 rpm, *b*-28 rpm, *c*-38 rpm, *d*-48 rpm. *Source*: From Ref. 26.

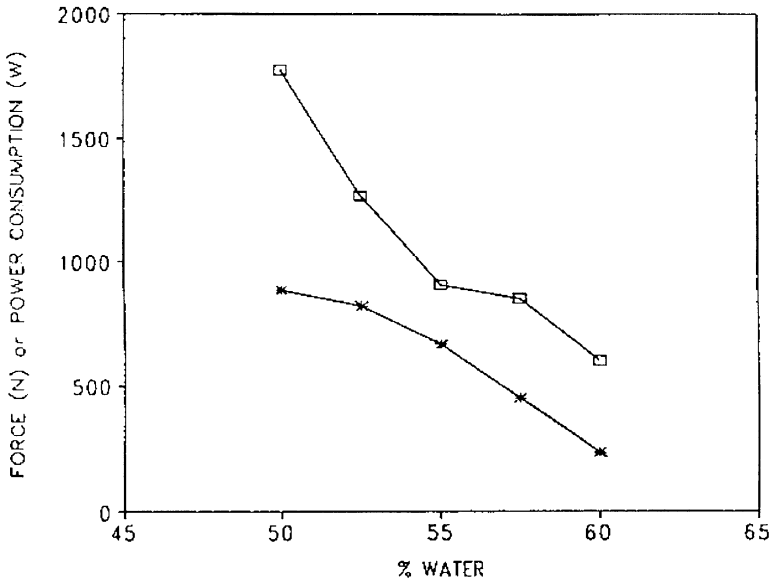

Figure 12 Influence of the amount of water on the extrusion forces (gravity feed extruder) and power consumption (twin screw extruder) on extrusion of MCC. □, gravity feed extruder (N); ∗, twin screw extruder (W). *Source*: From Ref. 37.

Figure 13. Screw extruders extrude poorly when the proportion of water soluble compounds, such as mannitol or lactose, reaches 50% or higher. Such formulations are better extruded with low-shear basket extruders (28). As the solubility increases from 5% to 30%, the percent of water needed for extrusion could decrease by up to 25%. This has implications for scale-up, as early lots of drug substance may have a different crystallinity or solubility profile than pilot lots.

On the other hand, the lack of adequate liquid–solid bonding between poorly water soluble, cohesive powders with high-yield stress, such as calcium carbonate and calcium phosphate, can also lead to high shear, temperature and force of extrusion resulting in fragile, and low-density extrudate. Serrated extrudate with a rough surface is termed "shark-skinned" and often the result of high-extrusion pressures and use of elongated screens or dies with smaller openings.

The formation of moisture gradients within the material during extrusion, resulting in migration of liquid from within the interparticulate spaces to surface of the extrudate, has been reported (40,25). At low initial moisture content, the friction within the chamber can result in higher temperatures leading to loss of moisture of up to 12% from the extrudate surface. This effect is more pronounced with A–A extruders.

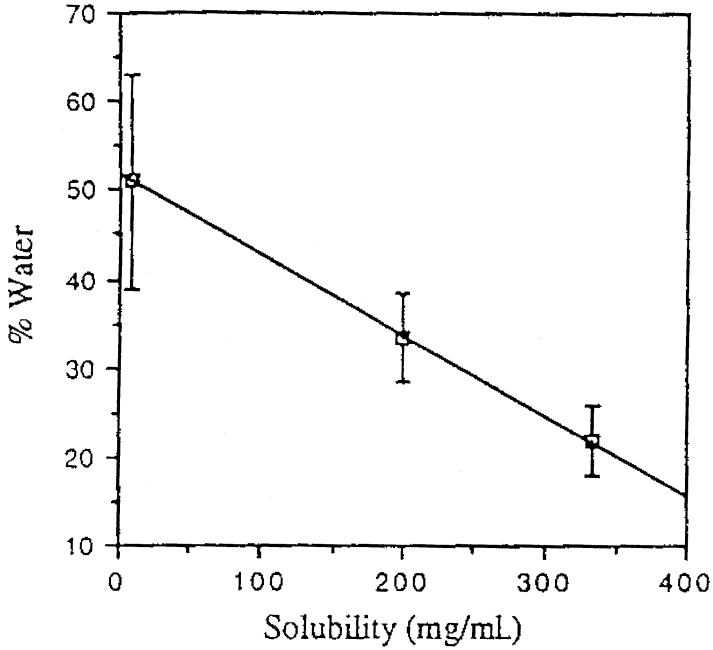

Figure 13 Effect of drug solubility on water required for 80% and 85% yields of pellets containing MCC. *Source*: From Ref. 39.

These studies point towards the need to optimize moisture content of the wet mass and extrudate by careful selection of formulation ingredients and type of extruder. A basket or gear/roll extruder is preferred for a very dense and moist wet mass, as it generates little shear and rise in temperature, while an axial or radial screw extruder which increases granule density and hardness is desirable for a wet mass which is less cohesive with poor binding.

The extrusion pressure could be further modulated by choice of dies or screens with appropriate L/D ratios. The pressure differential between points of die entry and exit due to viscosity for a Newtonian material moving within a cylinder is represented by Equation (4), derived from the Hagen–Poisuille expression for pressure drop in a pipe of constant diameter as (41)

$$\Delta P = 4\tau_w(L/D) \tag{4}$$

where ΔP is the pressure drop between die entry to exit points, dyne/cm^2, τ_w is the die-wall shear stress (viscous drag), dyne/cm^2, D is the die diameter, cm, and L is the die length, cm.

The use of screens with a larger L/D ratio in a low shear basket extruder can provide additional pressure for wet mass with low bonding strength.

A gravity feed extruder with $L/D = 2$ recorded (28) higher forces, compared to power generated from a twin-screw extruder with $L/D = 0.9$, upon extrusion of mixtures of MCC with either lactose or DCP. The extrudate from the basket extruder was denser with a smoother surface than that from the screw extruder. Similarly, material extruded through a screen with $L/D = 4$ in a basket extruder was denser than that with $L/D = 2$ (37). However, a smaller L/D ratio is preferred in an axial extruder. An improper L/D ratio could result in a loosely bound extrudate with large surface defects (37), resulting in a formulation less amenable to pelletization, as seen from Figure 14. Since the mean diameter of the pellet often approximates the diameter of the die used in extrusion, choice of the latter is also dictated by desired pellet size.

Screw speed is another variable that impacts extrudate quality via residence time. The effect of screw speed on extrusion shear stress is given (22) by the expression

$$\tau_w = m(V_b/H)^n \tag{5}$$

where m is the consistency index, n is the power law index, V_b is the screw velocity, and H is the channel depth of the screw.

Using a melt extruder with only feed screw elements (similar to wet extruder), a dense extrudate was obtained at 20 rpm that became soft and powdery at 50 and 100 rpm (42). At a lower speed, the material resides longer within the chamber and that could lead to greater homogeneity of binding fluid (water) in the material. In addition, the slower rate of extrusion provides a more uniformly dense extrudate.

From a formulator's perspective, the ability to modulate the rheology of the wet mass is critical to successful extrusion. Towards this end, MCC has often been used to facilitate extrusion. It is a dry binder used in tableting due to its plastic deforming ability that imparts tensile strength to a tablet. However, MCC has been used in wet extrusion for formulations containing a high amount of soluble ingredients (e.g., lactose and mannitol) or non-cohesive, poorly bonding inorganics, such as barium sulphate (35). With soluble materials, it lowers the yield force, thereby enabling uniform movement of the wet mass in the chamber, while with material like calcium carbonate, it provides the required cohesive or bonding strength for the extrudate. It has also been used in a co-processed (e.g., spray-dried) form with other polymeric binders, notably, sodium carboxy methylcellulose (Na-CMC), to increase density of the extrudate, though at a high-shear stress (39,43,44), especially in the presence of a soluble ingredient like lactose. Avicel RC-581®, a commercially available grade of co-processed MCC-Na-CMC mixture, enabled extrusion at a moisture level of less than 25% with improved yield, a moisture level too low for extrusion with only MCC (45). Upon wetting, these co-processed mixtures

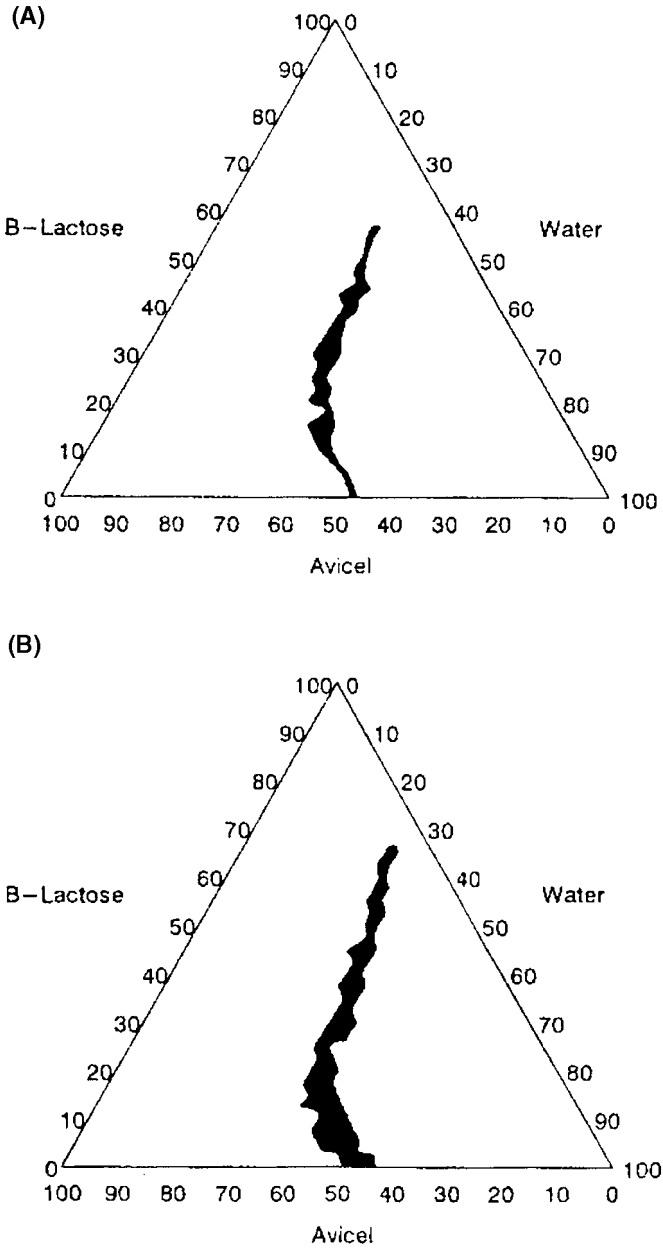

Figure 14 Phase diagrams indicating the zone where pellets of desired quality were obtained for lactose/MCC/water mixtures (**A**) zone for $L/R = 2$, (**B**) zone for $L/R = 4$. *Source*: From Ref. 38.

form colloidal dispersions that, depending on the concentration and applied stress, can range from a pseudoplastic sol to a thixotropic gel or a paste.

To summarize, while selection and scale-up of extruders is governed by extruder geometry, formulation, and process variables, secondary variables could be used to monitor the process on a continuous basis. Based on the reports thus far in the literature, the variables that seem to play a critical role in scale-up of extrusion are summarized in Table 7.

SPHERONIZATION

Spheronization is a process of forming spheroids from a given material. In the present context, the rod-shaped cylindrical pieces of extrudate are placed in a device called the spheronizer and "formed" into spheres when subjected to a high-speed rotation. The spheronizer basically consists of a grooved, horizontal friction plate rotating at a given speed within a stationary, vertical cylinder fitted with a door for discharge of the product. The cylinder is open at the top and has smooth internal walls. There is a clearance of about 0.25 mm between the edge of the plate and the inner wall of the cylinder. The grooves on the plate often are set to intersect at right angles to form "cross hatch" geometry and vary in size from 1 to 5 mm in width (Fig. 15). The diameter of the plate varies from 9″ to 15″ for laboratory scale equipment with an output of about 10 kg/hr to about 27″ for a production size unit with an output of about 100 kg/hr of wet spheroids. The speed of the plate could be varied from 100 to 1200 rpm, with the operation typically ranging from 200 to 800 rpm.

The success of spheronization depends on whether the extrudate can be suitably deformed into pellets. The ideal extrudate should break up into short, uniform rod-shaped pieces and have sufficient plasticity to be rolled into spheres by the action of the friction plate. In order that the granules

Table 7 Critical Variables in Scale-Up of Extrusion

Formulation	Process/extruder	Process monitoring
Moisture content	Configuration screw vs gear	Moisture content
Type and level of binder (e.g., MCC, NaCMC)	Rotational speed of extrusion head	Temperature
Soluble ingredients (e.g., drug, lactose)	Die or screen L/D ratio	Torque or force of extrusion
		Specific energy or power consumption
		Throughput rate

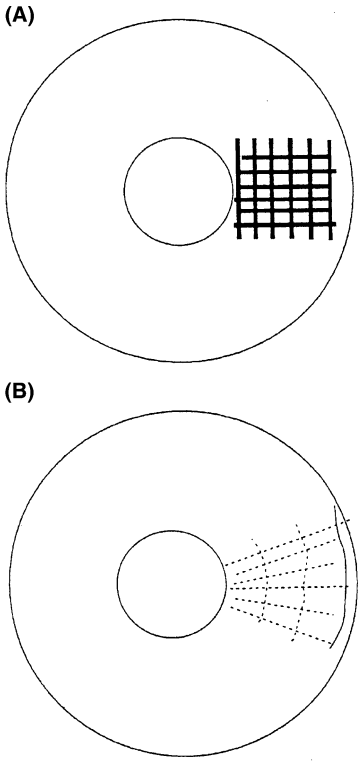

Figure 15 Geometry of friction-plate in spheronizer. (**A**) cross-hatch; (**B**) radial. *Source*: From Ref. 14.

be separate and discrete throughout the process, the extrudate should not adhere to itself or the plate and should retain enough cohesion so as not to break up into fine particles. Pellets typical of this process are dense and round in appearance with a narrow particle size distribution compared to granules from a conventional granulation process. The final pellet size and yield are dependent on such factors as diameter of the extrudate, and formulation attributes such as moisture content, rotational speed of the plate, and residence time in the spheronizer. An overview of spheronizers of varying scales and capacities is shown in Table 8.

Mechanistic Aspects of Spheronization

The earliest description of formation of spheres in a spheronizer was given by Reynolds (9) and Miyake et al. (46). Due to centrifugal acceleration and

Table 8 An Overview of Spheronizers of Varying Scales and Capacities

Company	Model[a]	Typical operating capacity (kg)	Maximum plate speed (rpm)
LCI	QJ-230	0.1–1.5	1800
	QJ-400	0.2–3.0	1280
	QJ-700	1.0–15	690
	QJ-1000	2.5–35	790
Caleva	Spheronizer 120	0.03–0.15	
	Spheronizer 250	0.1–1.0	
	Spheronizer 380	0.5–4	
	Spheronizer 500	1–11	
	Spheronizer 700	5–20	
Gabler	R-250	0.15–0.6	
	R-400	1–3	
	R-600	2–6	
	R-900	Upto 20	
NICA	S-320	0.2–1	600
	S-450	0.4–2	450
	S-700	2–10	300

[a]Number refers to plate diameter in mm.

deceleration, the material rotates in an annular shape against the wall of the spheronizer, thus generating a toroidal, rope-like motion. The collisions against the wall and the plate initially break the extrudate into short cylinders. The centrifugal forces generated by the moving plate and frictional forces due to the rough surface deform the broken cylinders into spheroids, as shown in Figure 16. Hypotheses of this conversion, based on a series of intermediates that include cylinders, cylinders with rounded ends, dumbbells, ellipsoids, spheroids with cavities, and finally, spheres, have been proposed (14,47). The intermediates are formed by the collision of pellets against each other, against the friction plate and against the wall of the spheronizer.

Zhang et al. (48) developed a model for spheronization process based on second-order kinetics and predicted the half life at which 50% of spheres (1:1 mix of acetaminophen-MCC) is >#14 mesh at 36 seconds. Based on this model, the process is essentially complete in less than five minutes. It has been theorized with the aid of high-speed photographic imaging that the shaping of pellets occurs by aggregation within 30–60 seconds of formation of the broken extrudate segments (49). Iyer et al. (26) obtained steady-state sphericity of pellets within three minutes of spheronization of mixtures of lactose and MCC, as shown in Figure 17 while Newton et al. (50) observed that roundness of pellets increased exponentially with number of plate revolutions. All these suggest clearly that spheronization is an

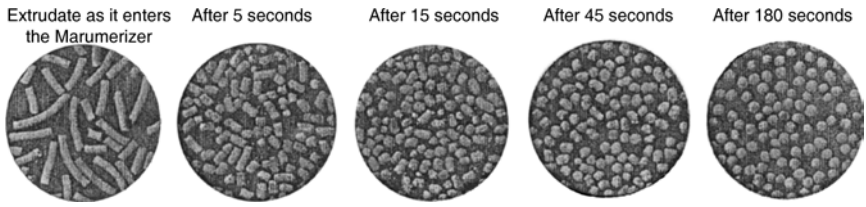

Figure 16 Example showing deformation of extruded pellets to produce spheres over time.

extremely fast process and the events happening in the first few minutes are critical to the quality of the resulting pellets. A primary goal in scale-up would then be to optimize the formulation and process variables, such that this initial "window" is prolonged in order have a more robust process. Operationally, a shorter time is often a goal in manufacturing. An optimal time of spheronization could then be identified.

The collision of the broken wet segments during spheronization can result in two effects: deformation and coalescence. The migration of moisture or soluble binders from the core to the surface of the pellets improves surface

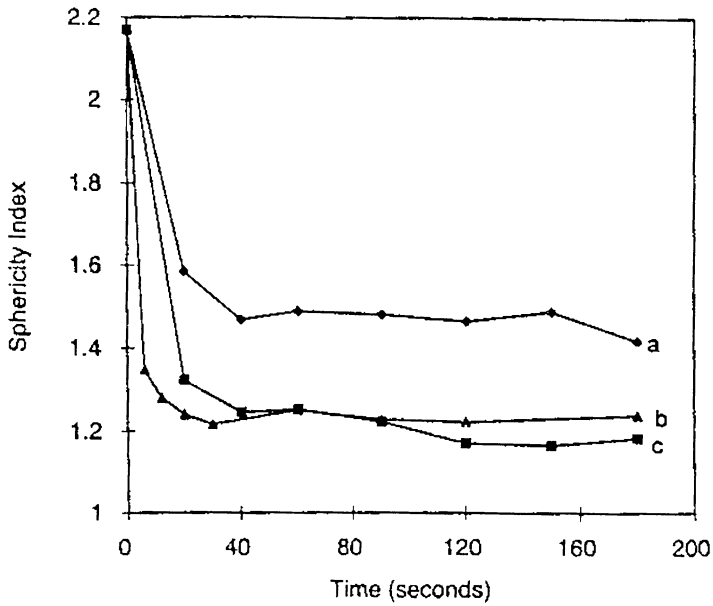

Figure 17 Effect of residence time on sphericity of pellets at varying plate speeds, *a*-350 rpm, *b*-680 rpm, *c*-830 rpm. *Source*: From Ref. 26.

plasticity, which is needed for deformation and rounding of the pellets (40,51). While deformation is desirable for shaping of the pellets, excess surface moisture could result in a high degree of liquid–solid bonding that leads to coalescence or uncontrolled "growth" of the spheronizing mass. An extreme case of this phenomenon is the formation of "golf-ball" sized pellets. A limiting agglomerate size, δ, may be defined (52,53), above which the tensile forces that separate particles due to centrifugal rotation exceed binding forces due to liquid saturation and surface plasticity, using a power law expression as

$$\delta = \mathrm{A}(k^{2/3}\sigma_{\mathrm{t}}) \tag{6}$$

where A is the constant, k is the agglomerate deformability, and σ is the tensile stresses on the agglomerate.

Low values of σ could result in aggregation or incomplete separation of pellets (e.g., dumbbells), as the forces may not be enough to overcome the liquid–solid bonding.

A modified expression for pellet deformation was given by Kristensen et al. (54,55) as

$$\delta^{2/a} = (\Delta L/L)^3/\sigma_{\mathrm{t}} \tag{7}$$

The left-hand side is a compliance parameter or bulk strain normalized for the centrifugal, gravitational, and inertial stresses exerted on the material during spheronization. The volume shape factor of pellets became closer to that of a sphere as the compliance of the extrudate increased, when measured in a creep test (56).

The challenge in spheronization is to affect surface deformation without coalescence of wet pellets in the early stages of the process. The binding forces due to free surface liquid and saturated liquid within cause deformation and rounding of pellets, while the separating forces due to inertial and centrifugal motion retard coalescence by keeping them apart. While formulation variables such as moisture content and binder level control deformation, the process and geometry variables, such as plate speed, diameter and residence time, assist in retarding coalescence. A balance of these stresses is critical to obtaining discrete, spherical pellets.

Among formulation variables, the moisture content particularly on surface of the material needs to be optimized. While excess surface moisture could lead to uncontrolled agglomeration, a dry extrudate can break up into fine powder. Upon spheronization for prolonged periods at high speeds, moisture gradients develop within pellets by migration from core to the surface. This is also a function of the concentration of dissolved solids and spheronizing time. The surface moisture could be lost over time, due to

evaporation and friction (57), unless the soluble materials migrate to the surface and form a moisture barrier that could prevent further loss. Since such phenomena are well established in drying it may be deduced, that some degree of drying occurs during spheronization.

End Point Determination

As described earlier, spheronization occurs via reduction of rod-shaped extrudate into smaller cylinders followed by deformation into spherical pellets. Since the pellet properties vary over a continuum, a mass of pellets is often defined by distribution of the properties on a suitable basis, such as number, weight, or volume. Limits or range of tolerance may then be assigned over this distribution and product acceptability or yield could be defined in this manner. A process end point, however, is difficult to convey, as the precise moment at which deformation is complete is unclear, since it involves changes in bulk properties of materials (shape, size, and porosity). The latter, in turn, are dependent on the type of extruder, size and mass of extrudate and spheronizing conditions, including residence time and plate speed (58–60). However, since deformation occurs from the collision of extrudate and pellets against each other, and against the plate and spheronizer wall, one or more outcomes of the collision events may be used to define the process. This could be a change in moisture content, impact force, pellet size, or wall friction; although techniques to measure these in a continuous manner during spheronization are not widely available.

The physical properties of pellets have been widely used to determine an acceptable yield of pellets. These include shape indices, size and size distribution, densities, pore volume and distribution, flow properties, and friability. Of course, drug release from the pellets is a critical parameter to be monitored in order to ensure potency and uniformity of drug distribution.

Sieve analysis using standard mesh screens is commonly used to determine particle size and size distribution of pellets and the reader is referred to standard texts for further information (61). Several types of densities have been defined for pellets based on interparticulate (void fraction) and intraparticulate pore volumes and include true, apparent, effective, bulk and tapped. The bulk and tapped densities may be obtained using simple devices, such as that used to evaluate granulations in tableting, while the true and apparent densities need more complex techniques based on mercury intrusion, gas flow, powder displacement, imaging or minimum fluidization velocity (62).

Since the desired shape of a pellet is a sphere, shape factors have been used to describe the pellets. These are characterized variously as sphericity, roundness, shape coefficient, elongation index, and aspect ratio (63–67). Using the volume diameter, d_v, and projected diameter, d_p, a good measure

of sphericity is the volume shape factor, α, given by

$$\alpha_v = \pi d_v^3 / 6 d_p^3 \tag{8}$$

$$d_v = (6/\pi \rho_g N_s)^{1/3} \tag{9}$$

where ρ_g is the apparent granule density and N_s is the specific particle number. The density ρ_g may be obtained by mercury porosimetry at low intrusion pressures, as Hg does not access capillary pores of $<20\,\mu m$ diameter under normal atmospheric pressure. The projected diameter d_p is a two-dimensional value obtained from microscopy. The volume shape factor equals $\pi/6$ for a perfect sphere, with smaller or larger values indicating deviations from sphericity. The more accurate surface-volume diameter, d_{sv}, is difficult to measure for porous, irregular spheronized pellets. A more commonly used two-dimensional sphericity is the roundness factor using microscopic imaging. Chapman et al. (68) characterized the roundness as the angle of inclination of a plane at which a particle would roll, termed as ''one plane critical stability.'' A summary of various shape indices is shown in Table 9.

It was already noted that the presence of excessive moisture on the surface of pellets during spheronization could lead to uncontrolled agglomeration. This effect could be minimized by adding adsorbents like colloidal silicon dioxide or talc to the spheronizing pellets, increasing viscosity of binding fluid and complexing soluble materials in the mixture. As in

Table 9 Typical Shape Indices of Pellets

Index	Expression	Sphere value
Sphericity	$\phi = d_{sv}/d_v$	1
Surface shape factor	$\alpha_s = S/d_p^2$	π
Volume shape factor	$\alpha_v = V/d_p^3$	$\pi/6$
Volume form factor	$K_e = \alpha_v.\sqrt{R.M}$	$\pi/6$
Surface volume shape coefficient	$\alpha_{sv} = S.d_p/V$	6
Shape factor	$\alpha = S./V^{2/3}$	4.837
Shape coefficient	$\alpha = (S_w.\rho.d_p) + (L/W)$	7
Aspect or elongation ratio*	$\alpha = d_{max}/d_{min}$	1
Circularity*	$\psi = P^2/4.\pi.A$	1
Roundness*	$K = 4.S/\pi.\ d_p^2$	1

Abbreviations: d_{sv}, surface volume diameter; d_v, volume diameter; d_p, projected diameter $= 0.99\sqrt{L.W.}$; S, surface area of pellet; V, volume of pellet; R, ratio of max. diameter d_{max} to min. diameter d_{min}.; M, ratio of width (W) to depth (X) of particle; K-S_w, specific surface area; *, obtained by microscopy.

extrusion, inclusion of MCC in a formulation can provide highly dense, less friable, and spherical pellets, depending on the drug loading. While elastic materials such as starch are more sensitive to moisture content during spheronization, MCC is easily deformable when its plastic limit is reached at a moisture content of 20% greater than its own weight (46,69). As in extrusion, co-processed forms of MCC with Na-CMC enable spheronization of formulations containing a high-drug loading of 50–80% (70). A spray-dried mixture of MCC with hydrophilic polymers was found to be less sensitive to moisture content, yielding pellets more spherical in shape than a physical mixture (43). The more adhesive polymers, such as NaCMC and HPMC, could inhibit deformation due to surface adhesion, resulting in lower sphericity values, while the more plastic and less adhesive HPC and PVP polymers provide greater roundness of pellets.

Based on the authors' personal experience (unpublished data) in formulating a low melting drug (m.p. of about 45°C), the selection of excipients was critical to both quality of pellets and scale-up of the process. In the presence of a low melting, hydrophobic drug, formulation with lactose exhibited significant sticking to the plate during spheronization. The addition of MCC and a surfactant reduced this sticking effect significantly. It was theorized that MCC holds significant water during spheronization, thus preventing moisture loss. This led to reduction in the percent of fines and subsequent sticking of the fines to the low melting drug. In addition, the surfactant reduced erosion at the edges by forming a smoother surface on the pellets. The addition of a small amount of vegetable oil significantly reduced product build-up and sticking, which was likely due to its lubricant effect that minimized particle-plate friction and formation of fines.

In general, extrudate with high-moisture content undergoes a greater degree of deformation, providing pellets with increased roundness, when spheronized for a longer time at a critical speed (59,60,67). It was observed earlier that sphere formation happens within a short time period and some moisture loss occurs during the high-speed rotation. This possibly means that although deformation (sphere formation) may be complete, it may be necessary to continue spheronization so as to keep the pellets apart until surface moisture content is reduced enough to minimize agglomeration. The particle size at this stage should approximate the extrusion screen size. Continued spheronization repeats this cycle, resulting in spherical pellets with a smaller particle size and narrower distribution. However, spheronization for very long time periods at very high speeds could lead to further moisture loss and dry pellets that may disintegrate into fine particles or a powdery mass, being unable to withstand the rotational and frictional stresses. Under such conditions, the choice of binder and binding strength is critical to maintain the physical integrity of the pellets.

The binding fluid can weaken the binder, as is seen with pectin when used with ethanol as the fluid. Ethanol reduces the swelling ability of pectin,

making the hydrocolloid ineffective, and resulting in spherical but weak pellets (63,71). The porosity of the pellets increased with increasing fraction of 2-propanol in water-propanol mixtures as binding fluid (72). An opposite effect was seen with chitosan that, when used in aqueous medium, retarded drug release and dissolution from the spheres (73). As in extrusion, the aqueous solubility of the drug was inversely linear to the amount of water required for optimal spheronization. Typically, poorly soluble drugs require more binding fluid and longer residence time for spheronization.

Process Control and Scale-Up

It is noteworthy to mention that all spheronizers across scales and manufacturers have the same basic design component, i.e., a rotating circular metal plate. A fully automated system, as shown in Figure 18, has two plates rotating in tandem to handle large batch sizes in a continuous operation. There

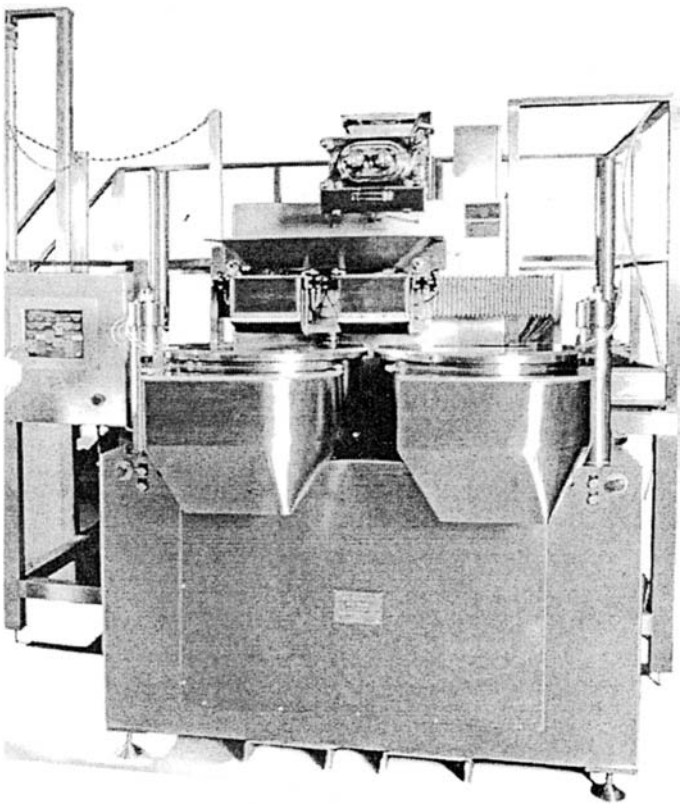

Figure 18 A fully automated, production scale twin spheronizer with an incorporated gear extruder assembly. *Source*: Courtesy of Caleva.

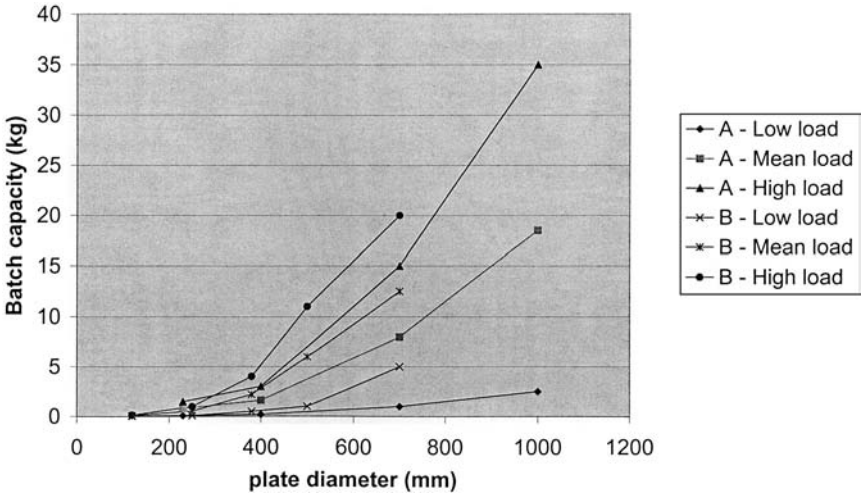

Figure 19 Comparison of material loads at high, low, and average values recommended by manufacturers A and B for spheronizers with varying plate diameters.

may be some variations, such as degree of plate roughness, but the simplicity of design makes spheronization easy to scale-up. At the same time, the wide variation in recommended batch size by manufacturers *A* and *B* for their respective spheronizers is shown in Figure 19. The range provided by vendor *A* is broader (0.1–15 kg) for a 700 mm diameter plate than that given by vendor *B* (5–20 kg) for the same size spheronizer. Further, the range becomes wider with increasing scale, suggesting that an optimal batch size needs to be developed for each application.

The two critical process variables are plate speed and residence time of pellets in the spheronizer, while the plate diameter is a geometrical variable that increases with material load.

For a given plate speed (S rpm), plate diameter (D), and spheronizing time (T), the scale-up may be based on keeping constant the number of revolutions, rotational distance, or peripheral velocity.

a. Number of revolutions (N)

$$N = ST \tag{10}$$

b. Peripheral velocity (V)

$$V = \pi DS \tag{11}$$

c. Rotational travel (X)

$$X = \pi DST \tag{12}$$

Fixed Number of Revolutions

Often, spheronizers are not available with variable motor drives, which means single or multiple but fixed speeds of operation. Figure 20 shows the impact of residence time for spheronizers of varying plate diameters from two different manufacturers when scaling is based on a fixed number of revolutions. The scale ratio based on output is 10–15×. Spheronization from source *A* in the larger unit at 690 rpm requires a process time of 20 minutes in order to maintain the same number of revolutions when scaling-up from the smaller unit at 1800 rpm for 7 minutes. The effect of surface moisture on pellet quality is more apparent due to the longer residence time at the larger scale. Spheronizers from source *B* seem less subject to the effect of residence time, since the plate speed over the entire scale is within a narrow range of 1500–2000 rpm. With this approach, scaling based on fixed speed implies a constant residence time. This would require the batch charge to be proportional in some manner to the plate diameter.

A drawback in scaling based on fixed number of revolutions is that it doesn't account for geometrical variable (plate diameter), which typically increases more than 3× for a 10× scale in batch output.

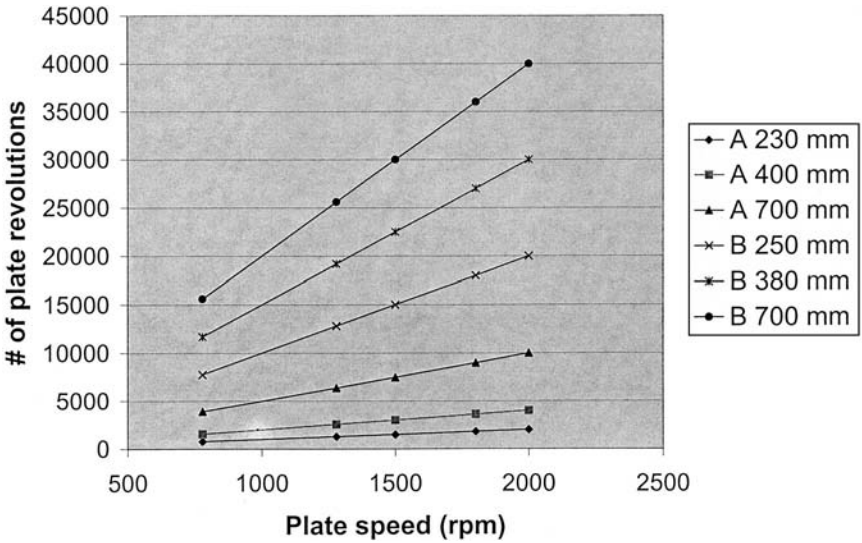

Figure 20 Plate revolutions simulated for varying spheronization times for three spheronizers of increasing scale from two manufacturers, A and B. Each simulation is at maximum recommended speed of operation. Each rpm in the legend for A or B represents a spheronizer of a specific diameter (scale).

Fixed Peripheral Velocity

The peripheral velocity, is a function of plate speed (process) and diameter (geometry) which vary across scale and across equipment from different vendors. It is analogous to the "tip speed" commonly used in granulation scale-up. Newton et al. (50) obtained pellets of similar quality while scaling-up spheronization at a constant peripheral velocity across a 25 × scale. A 0.2 kg batch size spheronized using a 22.9 cm diameter plate was scaled over a 125-fold range to 25 kg batch size, using a production spheronizer with a 65.6 cm diameter plate. The plate speed was decreased from 900 rpm at smaller scale to 340 rpm at larger scale in order to maintain a constant linear peripheral velocity at 424 cm/sec. The "one plane critical stability" angle and mean diameter of the pellets were comparable across the scales and decreased to the same minimal value as the number of revolutions was increased, as shown in Figure 21. This approach was also found to be somewhat independent of the mode of extrusion prior to spheronization (74).

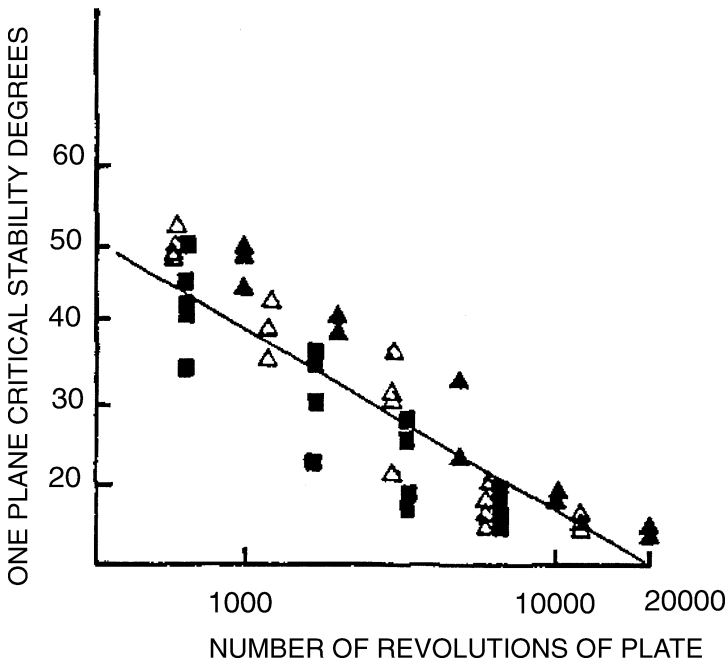

Figure 21 Change in the value of one plane critical stability with the number of revolutions of the spheronizer plate for granules from within the largest sieve fraction for batches spheronized on varying diameter plates: Δ, 22.9 cm; ▲, 38.1 cm; ■, 65.6 cm.

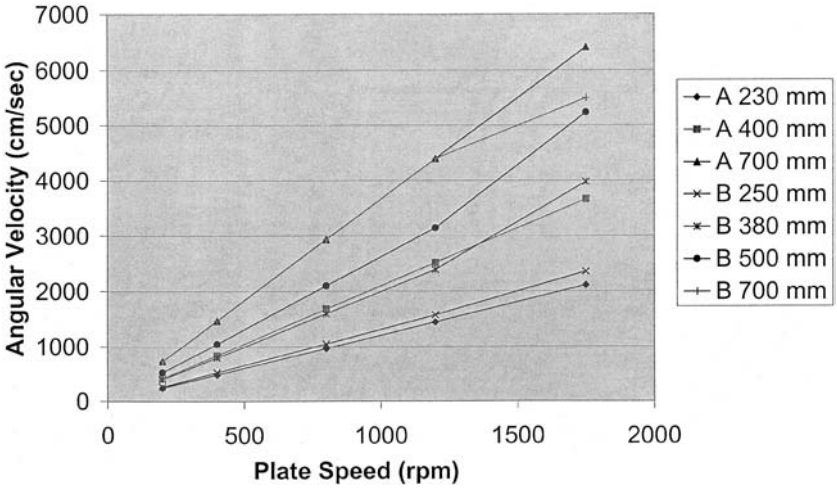

Figure 22 The angular velocities at varying plate speeds for three spheronizers of increasing scale from manufacturers, A and B. Each simulated run is at the maximum recommended speed of operation. Each number in the legend represents the plate diameter of a spheronizer from A or B.

Figure 22 shows simulated peripheral velocities at varying speeds for spheronizers of different diameters from two different sources. It is evident that this approach is independent of the manufacturer, since the only scale information needed is the plate speed, which is obtained from the plate diameter, and the peripheral velocity at the smaller scale that was used to obtain the target pellet attributes.

The Froude number is often used as a dimensionless index to scale-up a fluid whose flow field is governed by gravitational forces, among others (41). It is essentially a ratio of kinetic to inertial (gravitational) forces acting on a body. For a spheronizing particle, the kinetic parameter is the centrifugal force and is determined by plate speed and diameter while g represents the gravitational field. The Froude number is expressed as

$$\mathrm{Fr} = U/\sqrt{gL} \tag{13}$$

where U is the characteristic velocity, the peripheral velocity (m/s), g is the acceleration due to gravity (m/s^2), and L is the characteristic length, the plate diameter (m).

Since g is a constant, the scale-up factor becomes the centrifugal force as given by

$$F^{\mathrm{c}} = MS^2/D \tag{14}$$

with M being the material load. Based on this approach, spheronization of an ibuprofen product was scaled-up over a 10× scale with acceptable results (75).

PROCESS ANALYTICAL TECHNOLOGIES (PAT)

While the goal of PAT is to understand and control the manufacturing process, PAT itself is defined (76,77) as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. PAT helps profile the key information on a continuous basis, e.g., sensors on the blenders checking for blend uniformity, moisture and granule size growth during granulation, and particle size measurement during manufacture of suspension, provide valuable information to fingerprint the batch that, in turn, provides a means to control the process. The PAT initiative relies on four main components: data analysis, process analytical tools, process monitoring, and continuous feedback to assure product quality. In the foregoing discussions, we addressed the various critical variables based on mechanistic events and geometry (design) of components that influence these events. Based on the various on-line, at-line and in-line analytical technologies available to-date and the process considerations, the following aspects of extrusion-spheronization lend themselves to be evaluated under the PAT initiative.

Moisture Content and Content Uniformity

As shown in previous sections, moisture acts as a plasticizer and lubricant during the extrusion process and its control is critical to produce uniform and consistent pellets. Various on-line techniques that are available for measuring moisture are near infrared (near-IR) and thermal effusivity. The near-IR spectroscopy and its several variations, including near-IR chemical imaging, and Solid-state Acousto-Optic Tunable Filter Near IR Analyzers (AOTF-NIR) part of have found widespread acceptance as, PAT, due their non-destructive nature, sensitivity and flexibility of implementation and range of analyzing samples (solids, liquids, and powders) (78–80). The data collected by near-IR can be easily analyzed for moisture content (Fig. 23), as well as blend uniformity analysis, using various chemometric algorithms and "principle component analysis," thus making it a useful quantitative tool. For moisture analysis, the near-IR can provide accurate measurement down to 0.02%, while being capable of monitoring the granulation process requiring moisture as high as 50%. For blend uniformity analysis, the near-IR can be used to analyze fairly complex systems, provided that material is scanned by the instruments over several lots to establish the boundary conditions or failure points. Similarly, thermal effusivity, based on the heat transferability

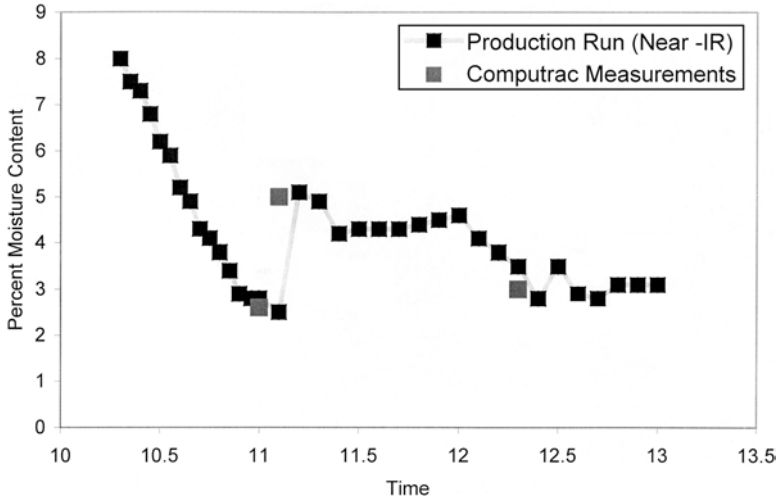

Figure 23 On-line moisture measurement during fluid bed drying vs. at-line measurement using Computrac®. *Source*: From http://www.brimrose.com/pharmal.html#anhor02.

of materials, can provide a mapping of material distribution in the powder mass. This non-destructive sensor is available for online monitoring of many processes, including moisture content, density, particle size distribution, and morphology (81).

The moisture determination is critical during granulation, extrusion, spheronization, and drying processes. Both of these techniques have been widely used in the granulation and drying processes, however, they can be easily adapted to extrusion and spheronization processes, as well to provide key information needed for process control. For example, appropriate sensors can be retrofitted onto the walls or covers of the processing equipment to enable comparison of the real time reading without removing samples from the process.

Particle Size and Size Distribution

The particle size and size distribution of granules (feeding material) and the pellets (dried pellets) are important process attributes that determine the process reproducibility and robustness. The measurement of wet granules (size and size distribution), extrudate size (diameter and length) and spheronized pellets (morphology, sphericity, size and size distribution) provide a useful insight in evaluating the role of process variables or formulation changes on the final product. The on-line measurement techniques range from Focused Beam Reflectance Measurement® (FBRM, Lasentec),

continuous in-process video microscope (Particle Vision and Measurement PVM®, Lasentec) to Insitec® (Malvern) (82,83). These techniques are being extensively evaluated for granulation process; however, as indicated earlier, they can be easily adapted to extrusion (for rods), spheronization (for pellets) and drying steps (pellet size) as well. They are capable of providing consistent data in the particle size range of 0.5–1000 μm; however, FBRM has been shown to work well for particles up to 2 mm and is one of the most widely used evaluation tool because of its application in chemical processes. The FBRM measures the distance as chord length, i.e., the distance between any two edges of the particle, with no assumption of any particular shape for the particle. The large number of measurements over a given period of time provides a statistically reliable measurement of the particle size and growth. A material prerequisite for using FBRM is that material should have some degree of backscattering. Most excipients and therapeutic agents used for extrusion-spheronization generally fall into this category.

Rheology and Flow of Wet Mass

An important consideration in the extrusion process is the flow of wet mass under pressure through the die. An appropriate control of the granulation end point is important to assure the reproducible processing of the batch during extrusion, as well as spheronization. Power consumption and torque measurements are commonly used for this purpose. Measurement of current can adequately express the torque for some DC operated motors and most extruders are equipped with this functionality to provide an indirect measurement of torque (83). The flow of wet mass in the extruder is generally monitored using at-line techniques such as ram extruder or torque rheometer. They provide useful information in assessing the effect of process and formulation variations on the processing. The flow of granules in extruders is regarded as a three-step process, consisting of compression, steady state flow and forced flow. A comparison of compression zone, steady state flow and forced flow zones for different formulations or granulation provides valuable information in optimizing the extrusion process (27,84). A typical force-displacement curve showing the three stages was shown in Figure 7 and can be used to track the product performance from small scale to various stages of scale-up. The mixer torque rheometer is also frequently employed in characterizing the wet mass and has been useful in establishing the boundary conditions for granulations in terms of providing reproducible pellets (84).

Another parameter of interest in the extrusion process is screen pressure, as that has been shown to affect the size of the final pellets as shown in Figure 24 (31). The extruder can be fitted with a suitable pressure transducer to monitor the pressure drop associated with extrusion. One such

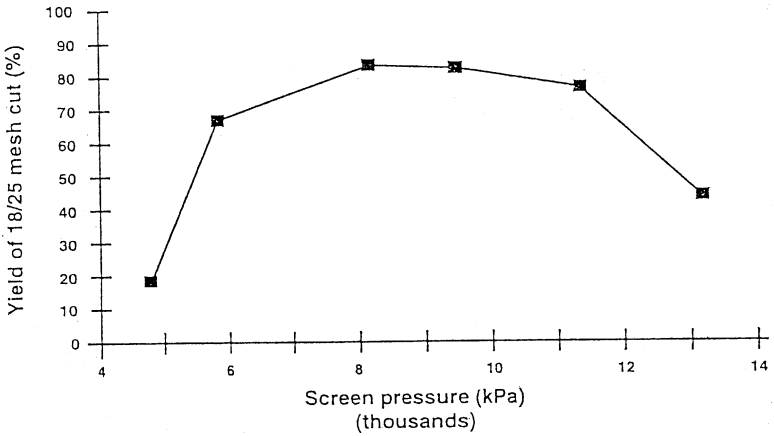

Figure 24 The effect of extruder screen pressure on the yield of particles within an acceptable distribution.

device available from Heastern (Dynisco Products) is shown in Figure 25, and allows on-line measurement of temperature and pressure. The measurement of back pressure at the extruder screen, pressure at the extruder outlet and the temperature provides an excellent opportunity for implentation of PAT. Nowadays, many extruders are equipped with a pressure transducer and digital indicator with hi-pressure shutdown, providing a safety feature, as well as a continuous profiling of the extrusion process.

SUMMARY

In summary, the extrusion-spheronization process has been successfully used in pharmaceutical applications and provides the formulator with a range of choices to manufacture pellet dosage forms. The process consists of five unit operations, dry mixing, granulation, extrusion, spheronization, and drying. While the process of extrusion and spheronization imposes stringent formulation requirements in terms of the various visco-plastic processes that it has to undergo, it is somewhat easier to manage from a scale-up perspective. The scale-up of extrusion can be accomplished using dimensional similarity while optimizing feed rate and efficiency. Several key process attributes, including formulation factors, equipment design, feed mechanism, and screen design, were presented. The successful scale-up of spheronization can also be predicted with careful evaluation of geometry, rotation speed, load, and time. As discussed within PAT implementation, on-line monitoring of key process variables, such as moisture, temperature, screen pressure, and torque, can help develop quality processes, thus assuring reproducible pellet characteristics,

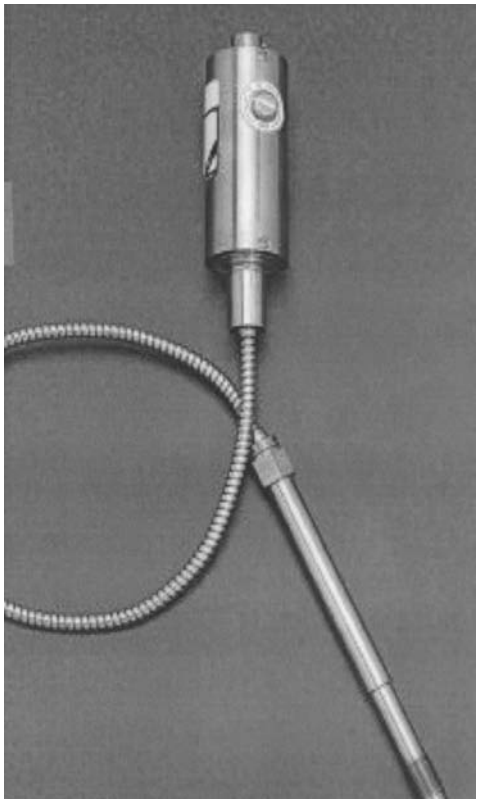

Figure 25 Integrated thermocouple and pressure transducer to measure temperature as well as pressure during extrusion. *Source*: Photo courtesy of Heaster Industries.

such as shape, size, and density. Thus, a good understanding of the mechanical process, formulation science and equipment geometry are essential to determine the critical variables that impact both extrudate and pellet properties.

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12

Scale-Up of the Compaction and Tableting Process

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INTRODUCTION

Tablets are a popular dosage form for oral delivery within the consumer health sector, as well as for ethical prescription products. Over 80% of marketed products are solid-dosage forms. The wide-ranging acceptance of tablet dosage forms probably stems from the fact that they are able to simultaneously satisfy biopharmaceutical, marketing, production, and patient requirements. Biopharmaceutically, tablets can be formulated for immediate or controlled release drug delivery. Additionally, tablets provide for gastric or enteric drug release, and multiple drug substances can be released from a single dosage form. Marketing groups also prefer tablets due to the number of options available for "branding" a product. For example, tablets can be formed in a variety of shapes and sizes, branded with embossing, debossing or printing, supplied in a multitude of colors using internal dyes and/or lakes or externally coated with films containing colorants. Production favors tablets over other dosage forms for their low cost of manufacture, which takes into consideration the cost of the raw materials, and the speed at which tablets can be produced. In the pharmaceutical industry today, tablets can be manufactured at rates of over one million units per hour. Although this rate of output is impressive, compression is still the rate-limiting manufacturing unit operation for many tablet product processes. Finally, patient convenience and preference for

tablets drive the market. They are portable, easy to swallow, and have the possibility of masking the taste of the medicine that is being taken.

The ultimate goal of many pharmaceutical formulation strategies is to achieve a marketable tablet dosage form, based on a balance between development cost and the attrition risk for the compound being developed. For new molecular entities destined to be commercial tablets, it is not uncommon for proof of concept studies or early clinical trials to use a powder-in-bottle approach or a hard gelatin capsule dosage form. In these cases, the attrition risk for clinical failure is high and it is not considered economical to develop a tablet early in the program. Specifically, tablets usually require more drug substance to develop, and this generally precludes many pharmaceutical companies from employing tablets in early clinical development. In many cases, a tablet is developed after the compound progresses to late clinical development (phase IIb or III), where the attrition risk is reduced. In these cases, the tablet development is usually coordinated for use in pivotal clinical studies, or linked with the clinical form used in the pivotal studies with a bioequivalency study. In those situations where the attrition risk is low for the compound under development, e.g., product line extensions or generic dosage forms, tablet development may be undertaken at the beginning of development.

In order to reduce associated costs, tablet development usually begins at a small scale. Indeed, many tablet products have progressed from a manual, one-at-a-time compaction process (Carver Press) through a single station compaction (e.g., F-Press, EK0), to a small-scale rotary tablet press (e.g., B3B, Betapress) and eventually to compaction on a production scale rotary tablet press (e.g., Fette 3090). It is this progression, from small-scale to large-scale compaction, that is the subject of this chapter. The ultimate test for the scale-up of a tableting process is the establishment of a successful, routine manufacturing process within a production environment. There are many objective criteria associated with commercial manufacture that can be measured and modeled with statistical process control, e.g., weight uniformity, compaction force, content uniformity, and tablet properties (hardness, thickness, friability, etc.), as well as other, more subjective criteria, e.g., appearance, sticking, picking, capping, lamination, etc., that are just as important but more difficult to model.

To address the issue of the scale-up of the tablet compaction process, this chapter will review the following: (1) compaction, (2) predictive studies, (3) scale-up/validation process, (4) case studies, and (5) process analytical technologies.

COMPACTION PHYSICS

Compression and Consolidation

The compaction process has been studied extensively and macroscopically and it is well characterized. This is advantageous, since any understanding of the

tablet scale-up process requires a solid understanding of compaction science. Typically, tableting involves two main processes: (1) compression and (2) consolidation. During compression, the primary particles are rearranged in a more efficient manner, densifying the material by eliminating air within the powder matrix. Consolidation is an increase in the mechanical strength of the powder matrix as a result of particle/particle interactions. The nature of the materials comprising the powder particles, and the magnitude, duration and translation profile of the applied force (including the relaxation profile and ejection profile), will dictate the strength of the resulting compact. Rearrangement of particles within the die, as well as compaction, will have an effect on many of the final tablet properties, e.g., tablet strength, lubricity, dissolution, etc.

Stress-strain type equations have been developed for the compaction process, which help provide an understanding of the mechanisms involved in forming a tablet, as well as allowing for the prediction of compaction results. This predictive power of the compaction process is the basis for many scale-up approaches. However, there are compression and consolidation process aspects which are dependent on manufacturing scale, e.g., speed-sensitive materials, and this results in many problems encountered in transferring a technology to production scale. Unfortunately, these scale-sensitive processes have not been as extensively studied, and are less understood.

The compaction process can be described by a variety of force (or pressure)-displacement profiles, such as force versus time, force versus tablet porosity, and force versus tablet properties (hardness, friability, dissolution, etc.). The effect of compaction speed on a variety of tablet properties can also be studied.

From a practical standpoint, the compaction profiles can be separated into those that include displacement measurements of the powder bed during compaction, and those that do not. Typically, displacement measurements during compaction are used to define relationships between compaction force/pressure and the resulting tablet porosity/density. Heckel plots have been widely discussed and presented in the literature (1–5). The shape of the Heckel plot has been used to describe the type of deformation mechanism (brittle and/or elastic/plastic) occurring during compact formation (6–9). Characterization of the deformation mechanism of a material is useful in predicting the tableting process at a different scale, where press speeds result in different dwell times and contact times. Viscoelastic and plastically deforming materials may be particularly sensitive to changes in speed that occur on scale-up.

Force measurements made without displacement values are still useful in identifying the dependency of tablet hardness (and other associated characteristics) on compaction force, and also the effect of the tablet press compaction speed on tablet strength (influence of dwell time/effective

contact time). Dwell time dependency is a major scale-up factor for the tableting process, and this dependency at small-scale is useful, although the actual commercial dwell time is not always achievable on instrumented, small-scale tablet presses.

In addition to these primary force measurements, tablet take-off force, ejection force, and radial die wall force have also been investigated. Tablet take-off force gives an indication of the sticking/picking tendency of a formulation. Ejection force is important in determining the lubricity of the formulation. A certain level of lubrication is required to ensure efficient tablet ejection from the die wall and can be affected by the scale of manufacture due to differences in the ejection profiles and dwell time that exist between small- and large-scale equipment. Also, the lubricity may change due to other manufacturing process scale-up effects (powder blending), and other tableting processes (filling into the die). Hence, the final powder blend may behave differently despite an identical compaction environment. Radial die wall measurements can be useful in determining the residual die wall force exerted on the tablet after compaction. High residual die wall forces are implicated in tablet capping tendency, and may also be indicative of insufficient lubricity of the powder blend.

Excipients

Successful scale-up of the tableting process also requires control of the raw materials used in compaction. Typically, pharmaceutical excipients vary in their physicochemical properties, which result in batch-to-batch variations. The tableting process, especially direct compression processes where there is limited raw material alteration before compaction, is susceptible to raw material variation, which may be magnified upon scale-up. Compaction science affords the ability to "fingerprint" raw materials, including the drug substance, to determine if the same compaction properties will be observed from batch to batch. This also allows for a rational approach for determining alternate vendor sources of the same materials.

The excipients selected during formulation development will affect many properties of the final dosage form, including the strength of the tablet, dissolution release profile, the uniformity of the dosage form and the size of the tablet. Each excipient has a specific function and excipient selection will be made based on the characteristics of the drug substance (e.g., wettability, solubility, stability, bulkiness, compactibility, etc.) as well as the final manufacturing process that is selected (e.g., direct compression, roller compaction, or wet granulation).

The deformation properties of the drug substance and excipients will have a direct influence on the strength of the tablets that are produced. During the compaction process, as the powder flows from the hopper into the dies, the only force acting on the particles is due to the particles themselves. Then as the punches enter the dies, initially very low pressures are

applied, causing particle rearrangement. When particles can no longer move, they begin to deform as pressure increases.

The type of deformation that occurs will depend upon the material's inherent properties and the amount of force being applied. Deformation can be described in three main ways, elastic, plastic, and brittle fragmentation, but it is important to realize that these are "idealized" deformation mechanisms—most real materials are some combination of two or all three mechanisms.

Elastic deformation is a reversible process, whereby, if the applied load is released before the elastic yield value is reached, the particles will return to their original state. Plastic deformation and brittle fragmentation are non-reversible processes that occur as the force on the particles is increased beyond the elastic yield value of the materials. Brittle fragmentation describes the process where, as the force is increased, particles fracture into smaller particles, exposing new, clean surfaces at which bonding can occur. For plastically deforming materials, when the force is removed, the material stays deformed and does not return to its original state. Plastic materials are also known as time-dependent materials because they are sensitive to the rate of compaction. We can also speak of viscoelastic-type materials which stay deformed when the force is removed, but will expand slowly over time.

By characterizing the deformation properties of the drug substance, one can select excipients that complement the drug substance so that a tablet with sufficient strength is produced. In the final dosage form, tablet strength must be balanced with the ability of the tablet to release the drug substance (disintegration and dissolution).

Despite the progress of compaction science to date, it is still not possible to predict the scale-up success of a candidate formulation. Today, the only proof of success is still the establishment of a commercial manufacturing process. This could be considered the ultimate use test. However, failures upon scale-up that can be traced to raw material changes in compaction properties, dwell time effects during compaction (press speed) and capping associated with excessive residual die wall forces can be avoided by developing well characterized, robust formulations and processes prior to scale-up. The remaining problems are those connected with the transport of the powder blend from the blender to the tablet die, the filling of the die, the environmental conditions of the production floor (temperature, humidity, vibrations, lighting, etc.) and changes resulting from scale-up effects for other unit operations (blending, granulating, drying) or compaction equipment (tooling). All of these issues should be kept in mind while developing a tablet formulation and process. Proper engineering controls can also be used to minimize the impact on scale-up.

PREDICTIVE STUDIES

As mentioned previously, scale-up effects are important for the tableting process since most tablet development occurs at small-scale to minimize

costs. Although this is true for most, if not all, tablet development, the time spent on small-scale equipment before moving into a production environment, and the actual size of the small-scale equipment used initially can vary greatly. In today's competitive environment, speed-to-market plays an important role. Therefore, any approach that can reduce development time must be considered. In this vein, it can be argued that for tablet development involving line extensions for established products, e.g., a new strength, material costs may be more manageable, and it may be possible to run full scale batches as development batches. In this case, predictive scale-up studies are less important, although still useful.

Predictive studies that have been employed for the scale-up of tableting processes can be grouped into several areas. First, dimensional analysis can be used, where equations of known dimensional relationships can be used to construct a dimensionless correlation. A dimensionless correlation is, by definition, independent of scale. Tablet and flow indices fall into this category. Second, compaction simulators have been designed for single-tablet studies which mimic the compaction environment encountered during commercial production. Hydraulic compaction simulators, as well as the mechanically driven machines (i.e., Presster™, Metropolitan Computing Company and Stylecam, Medelpharm), are available for such studies. Third, small-scale-tableting studies identifying and investigating the critical parameters, using design of experiments (DOE) and other statistical or trial and error approaches, are conducted and scale-up factors are applied for commercial production.

Indices and Related Parameters

Indices are dimensionless parameters derived from various mechanical and physical properties of the tablet blend and resulting compacts. Mechanical properties typically measured include indentation hardness (kinetic and static), elastic modulus, and tensile strength (10,11). Physical properties include particle size, shape, and size distribution, density (true, bulk, and tapped), flow properties and cohesive properties.

The indices developed from these mechanical and physical properties are useful in describing and predicting tableting properties (12), including the associated flow of the tableting mixtures. Of these, the indentation hardness describes the ability to form compacts during compression, the elastic modulus determines the amount of elastic recovery and, hence, lamination potential of the tablets and the tensile strength determines the overall strength of the formed compact (13,14). Although indices are typically used to aid formulation development of tablets, their dimensionless properties allow the indices to be useful in predicting the scale-up behavior of tablet formulations and processes.

The angle of repose of a powder blend, effective angle of internal friction (EAIF) from shear cell measurements, and the mean time to avalanche (MTA) in powder cohesivity tests are useful for assessing the flow of a tableting mixture at various scales (15–18).

Hiestand has developed many indices that are useful for tablet formulations (16–18). These include the frequently cited brittle fracture index (BFI), the best-case bonding index (BI_b), the worse-case bonding index (BI_w), and the viscoelastic index (VI) (15,16).

The BFI is defined as shown in Equation (1).

$$BFI = 1/2(TS/TS_o) - 1 \tag{1}$$

This index describes the potential of the tablet to cap and laminate, and is related to the ability to relieve shear stresses within the compact via material flow. In Equation (1), TS equals the tensile strength of the normal tablet and TS_o is measured from a tablet with a hole in its center, which simulates a defect.

The BI_b and BI_w are defined as shown below in Equations (2) and (3), respectively. Both indices describe the bonding ability of the tablets by using the ratio of tensile strength and indentation hardness. However, BI_b is determined at low-indentation speed (H_0) and BI_w is determined at high speed (H_{10}). Hence, BI_w is considered more indicative of actual tableting conditions, whereas BI_b relates to slower compactions speeds typical of development or roller compaction processes.

$$BI_b = TS/H_0 \tag{2}$$

$$BI_w = TS/H_{10} \tag{3}$$

A large difference between the two indices may predict sensitivity to scale-up of the tableting process relating to dwell time of the machine. This tendency, is described as the VI, as shown in Equation (4). However, no correlation of this index to scale-up has been shown to date in the literature.

$$VI = H_0/H_{10} \tag{4}$$

A common powder flow index includes the Carr Index, calculated as shown in Equation (5). In this index, the ratio of the difference of the tapped versus bulk density to the tapped density is given. This ratio, multiplied by 100 to convert to percent, indicates poor flow when the index equals 20 or greater.

$$100(D_T - D_B/D_T) \tag{5}$$

where D_T equals the tapped density and D_B equals the bulk density.

For example, the use of a shear cell for determination of flow properties (cohesion) has been conducted as shown in Figure 1. Despite some variability, the shear cell values obtained correlated well with the Carr Index.

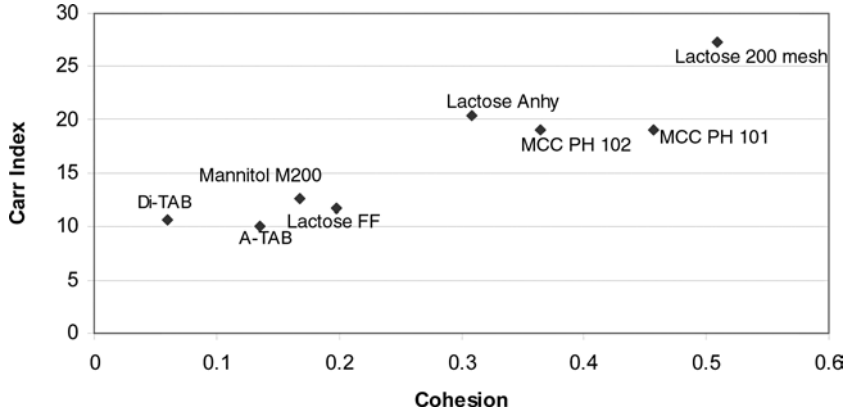

Figure 1 Shear cell index versus Carr Index.

The prediction power of the shear cell measurement for powder flow as judged by tablet weight uniformity is shown in Figure 2. Discrepancies, especially among powders with good flow, are observed.

Although proven useful for formulation development, the various defined indices and associated mechanical and physical properties have not been shown to be able to conclusively predict scale-up performance of

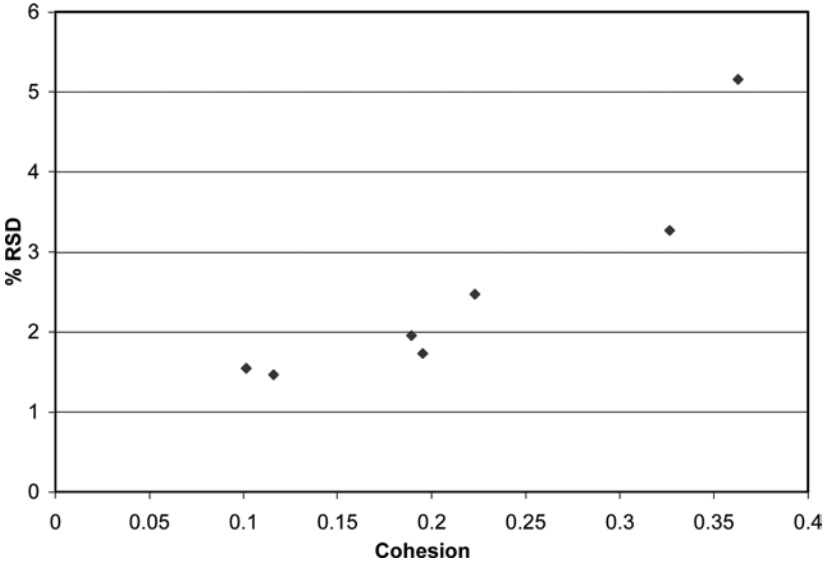

Figure 2 Shear cell index versus weight uniformity from a B3B tablet press.

a tableting mixture. Additionally, the measurement of some indices can be time-intensive, and sensitive to experimental techniques. Indices, however, can be an integral component of an overall scientific approach to robust tablet development and scale-up to production.

Simulation

The use of compaction simulators was first reported in 1976. Since then, a variety of simulators have been developed. Hydraulic simulators, as well as mechanical simulators, are available to characterize raw materials, drug substances, and formulations, as well as to predict material behavior on scale-up. The appeal of simulators is due to the fact that they purport to provide the same compaction profile as experienced on a tablet press while using only gram or even milligram quantities of powders. Compaction simulators can achieve high speeds, as would be experienced on a production tablet press, and can be instrumented to measure a variety of parameters, including upper and lower punch force, upper and lower punch displacement, ejection force, radial die wall force, take-off force, etc. Summaries on the uses of simulators and tablet press instrumentation can be found in (19,20).

Compaction simulators can have utility throughout the life of a drug product. Some of the uses for a simulator in pharmaceutical development and production are listed below:

- Preformulation
  - Characterize the drug substance regarding deformation properties, compactibility, sticking tendency, ejection force, etc.
  - Compare compaction properties of different salt forms, polymorphs, or hydrates.
- Formulation
  - Aid in excipient selection (based on deformation properties).
  - Compare compaction properties of formulation variants.
  - Develop robust formulations by simulating production machines or running with dwell times similar to production tablet presses.
- Production
  - Troubleshooting production problems at a small-scale.
  - Evaluating changes in drug substance (particle size, manufacturing site, and manufacturing process), excipient sources, or processing conditions.

Production machines are usually instrumented for force measurement in order to control tablet weight. However, the entire force-time profile and punch displacement are not usually measured in production, so it is difficult

to make a direct comparison to data that may have been produced using a simulator. One option would be to take a sample of material from production and run it on the simulator and compare the tablet properties to previous small-scale batches. Additionally, the force-hardness plots can be compared between the compaction simulator and the production press if the production machine is instrumented for force measurement.

The following paragraphs provide several examples for uses of a compaction simulator during development and scale-up. In these cases, the Presster was used as the compaction simulator.

Example 1

In order to determine how useful the Presster would be in predicting the behavior of a formulation on a production tablet press, it was decided to do a retrospective evaluation of two products that are routinely manufactured in production. The conditions used for manufacturing the two products in production were simulated on the Presster and the results are presented in Figures 3 and 4.

Figure 3 displays the results for a wet granulated product run at three speeds and three forces in production. The same speeds and similar forces were used on the Presster. Thirty tablets were produced at each speed. It can be seen that although the absolute hardness values differ by 1–2 kP in some cases (most likely due to differences in the two hardness testers used), the range of the window for the hardness values is comparable between the two machines.

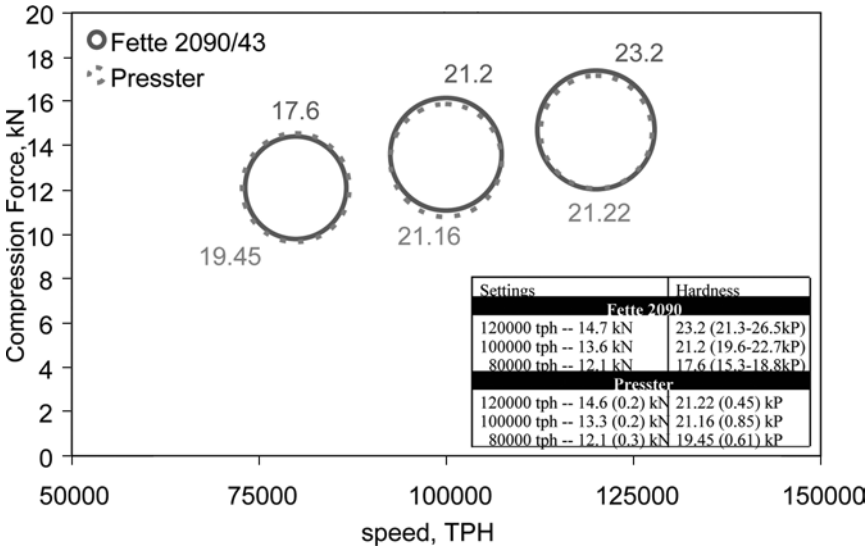

Figure 3 Ovaloid tablets (~17 mm length), wet granulation hardness (kP) profile.

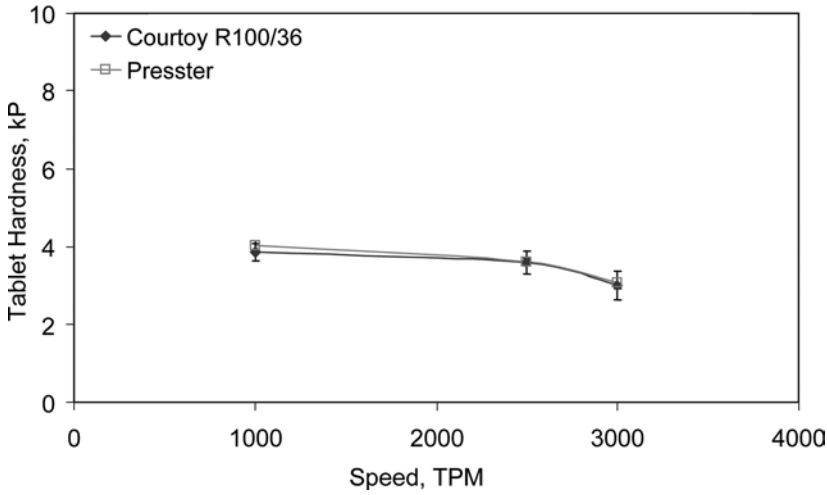

Figure 4 Comparison of a production compression profile (Courtoy R100/36 stations) to a Presster compression profile simulation.

In Figure 4, data from a low dose wet granulation formulation produced in production on a Courtoy R100/36 is compared to the Presster tablet hardness data. The force-hardness data from the two machines was comparable.

From these two examples, it was concluded that the Presster was able to accurately predict the results that were observed during routine production and would be useful to predict formulation behavior on scale-up.

Example 2

After scale-up into production, it was determined that an increase in moisture content would improve the formulation stability for a high dose wet granulated product. It was decided to use the Presster to predict the results that would be obtained in production when the moisture content of the final blend was increased. Blends with three moisture levels were compressed at two forces. As shown in Figure 5, as moisture content increases, tablet hardness increased. The dissolution profiles for the tablets with different moisture levels were compared and found to be within specification, indicating that raising the moisture content in the final blend should result in acceptable tablets in production.

The Presster successfully predicted the results in production and no issues were observed upon scale-up with the higher moisture content formulation.

Example 3

This example is for a direct compression product. The drug substance manufacturing process was found to have an influence on the compaction

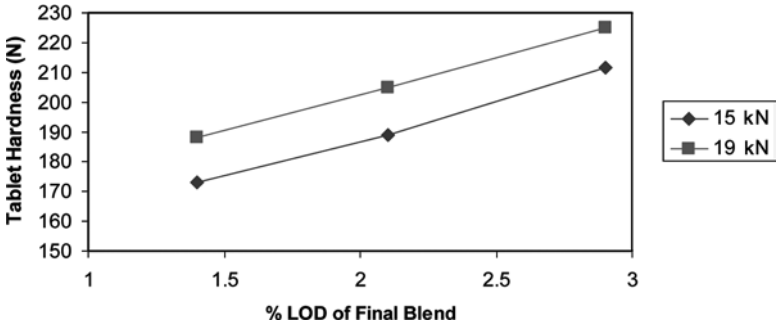

Figure 5 Effect of LOD on formulation A (high dose) compression at two different forces.

properties of the drug product and Chemical Operations wanted to change the manufacturing site of the drug substance prior to scale-up. Development batches were manufactured with small samples of the drug substance from both the new site 2 and the existing site 1.

In Figure 6, if you compare the compression profiles of the drug substance from the two sites, the new material is actually forming stronger compacts than the original material.

The impact of the drug substance particle size distribution was also evaluated. No significant effect on compact hardness is observed, as shown in Figure 7.

Example 4

This is an example from a high dose, roller compaction formulation. A new strength for an already validated product was being developed. Final blend 2 was used during development to set the ranges for the IPC specifications. Upon scale-up of the new strength into production, specifications for

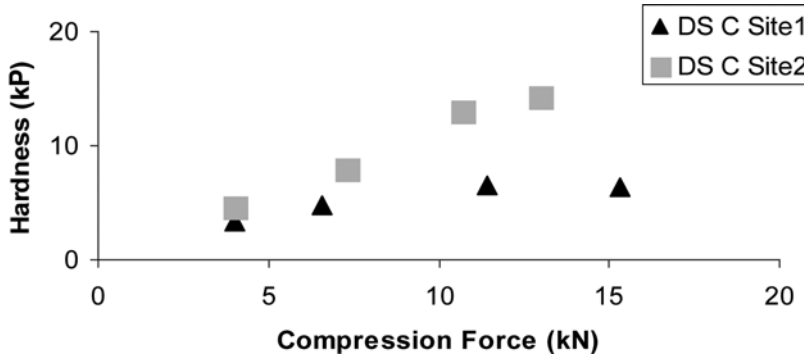

Figure 6 Comparison of manufacturing sites.

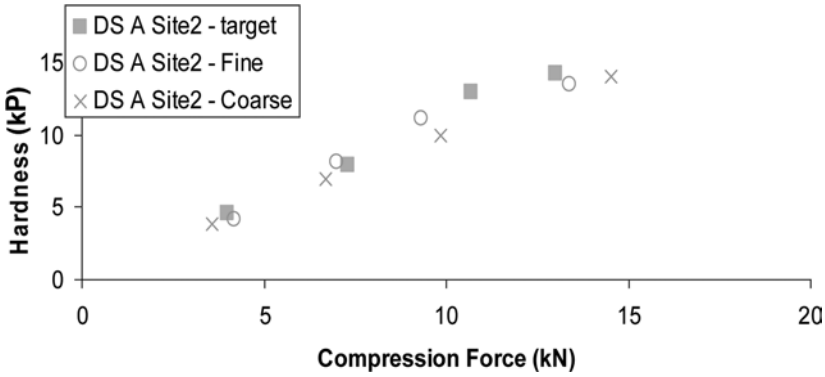

Figure 7 Compaction profile of DS—effect of PSD.

hardness did not meet requirements that had been set during development. Samples of the final blend 2 used for development and the final blend 1 used in the scale-up batch were compared on the Presster and it was determined that there were differences between the two blends. Further investigation revealed that final blend 1 was atypical to what is normally observed in production (Fig. 8).

Pilot Work

Pilot phase development allows the formulator to evaluate critical process parameters of compression essential for trouble-free production. Typically, DOE are used to evaluate the effects of process variation on the resulting tablet

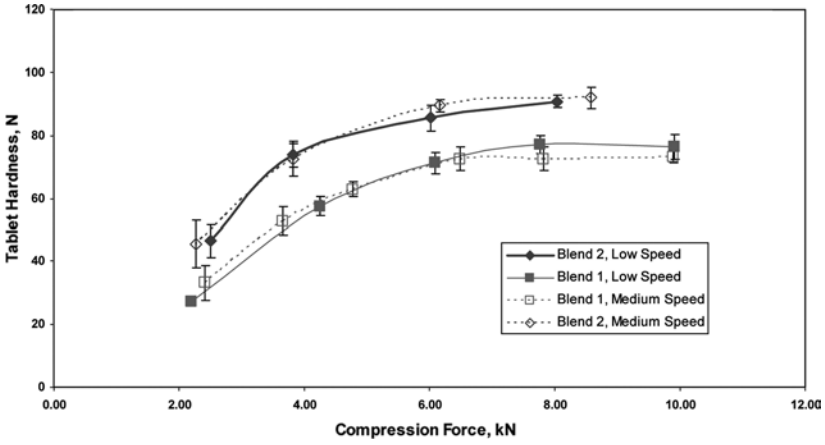

Figure 8 Comparison of manufacturing sites.

hardness, thickness, friability, disintegration, dissolution, and content uniformity. Compression is the cumulative result of several up-stream processes. Blend time, lubricant level, particle size distribution, disintegrant level and granulate (binder level, solvent quantity, solvent addition time, and granulation time) all affect the ability of a powder blend to form a consistent compact.

Tableting speed or dwell time is the only scale-up parameter typically known. Dwell time is defined as the time when the compression wheel is in contact with the flat portion of the punch head. Dwell times differ significantly during scale-up and between tablet presses. On smaller development presses, the dwell times can range from 0.08 to 0.50 seconds. However, on large production type tablet presses, the dwell times can be as low as 0.005 seconds. These values are calculated for standard TSM type B tooling. This difference in dwell time affects the peak height during the compression event. Longer dwell times result in shorter peak height and vice versa. The peak height plays an important role during scale-up. Higher peak forces can affect high-speed production presses, such that tooling, cams, and pressure roll wheels wear faster as compression forces increase. Again, decreasing dwell times and increasing compression forces can cause problems, such as lamination, capping, and die binding. All these aspects must be considered during development to ensure that the process will perform as expected during reduced dwell times encountered in the production environment.

Below is an example of pilot work in support of a scale-up to production. In this example, the final blend was compressed on a 16 station rotary Beta press using ovaloid tooling. A compression profile, as shown in Figure 9, was generated. The speed of the tablet press was fixed at 78 rpm. Forces ranging from 8 to 28 kN were evaluated. Lamination was observed at forces greater than 25 kN. The curve was relatively flat between 15 and 25 kN forces with hardness ranging from 175 to 215 N.

Friability measurements were done for cores compressed at hardness ranging from 154 to 216 N, as shown in Figure 10. Data show that cores

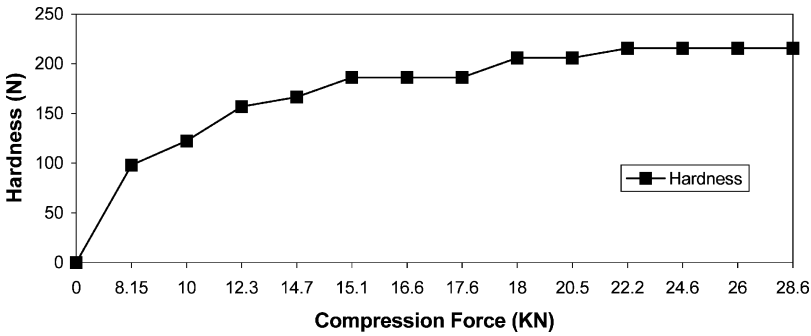

Figure 9 Compression profile.

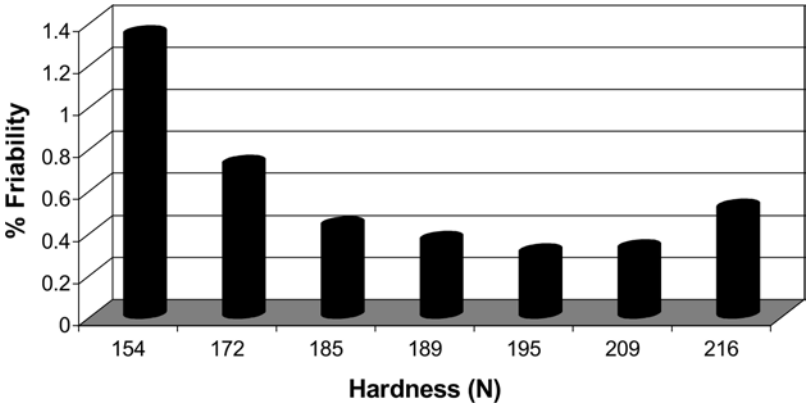

Figure 10 Friability evaluation of cores compressed at various hardness.

compressed between 170 and 215 N hardness (15–25 kN force) resulted in acceptable friability. Based on friability data, a target hardness of 190 N (170 and 210 N range), which corresponds to 18 kN force (16–20 kN), was used to compress the remainder of the batch.

The mass flow requirement of a production press requires further consideration during early development. The dry powder blend or granulation is expected to flow under the influence of gravity within a storage bin containing from 100 to 1200 kg of material. Once outside the tote, the material must flow through a series of distribution pipes into the hoppers. Figure 11 shows an analysis of flow for a wet granulation process at pilot scale. Here water amount and lubricant were optimized to improve flow.

Another example of the use of DOE during pilot studies is the study of factors affecting the ejection and take-off force. Measurement of ejection force and take-off force will determine if the formula is sufficiently lubricated. Ejection force is measured as an indication of the release of the tablet from the die wall forces, and the take-off force related to the adhesion forces to the punch face. Take-off force is an appropriate measurement to determine if a formula has a tendency to stick. Based on these designs, an optimal formula, including the lubricant level, and process can be predicted for scale-up (Figs. 12 and 13).

A second flow measurement to be considered during scale-up is the ability of the granulate/powder to fill the dies. This can most efficiently be monitored by punch force variability and individual core weight measurements. Acceptable weight control (<3% RSD) and force (<5% RSD) may be masked at slower compression speeds typically used for development or when a tablet press is not fully tooled. Production operations will tend to run at the high end of any validated range, so flow must be consistent from batch to batch.

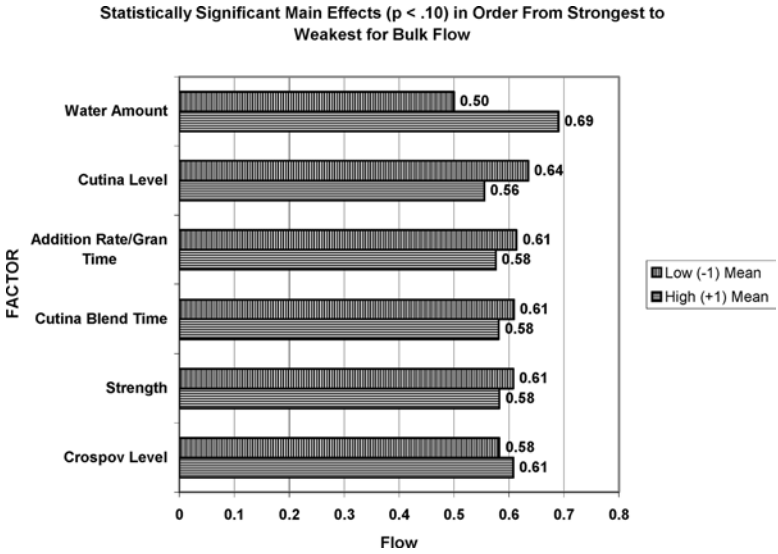

Figure 11 Factors affecting flow of a tableting mixture prepared by wet granulation.

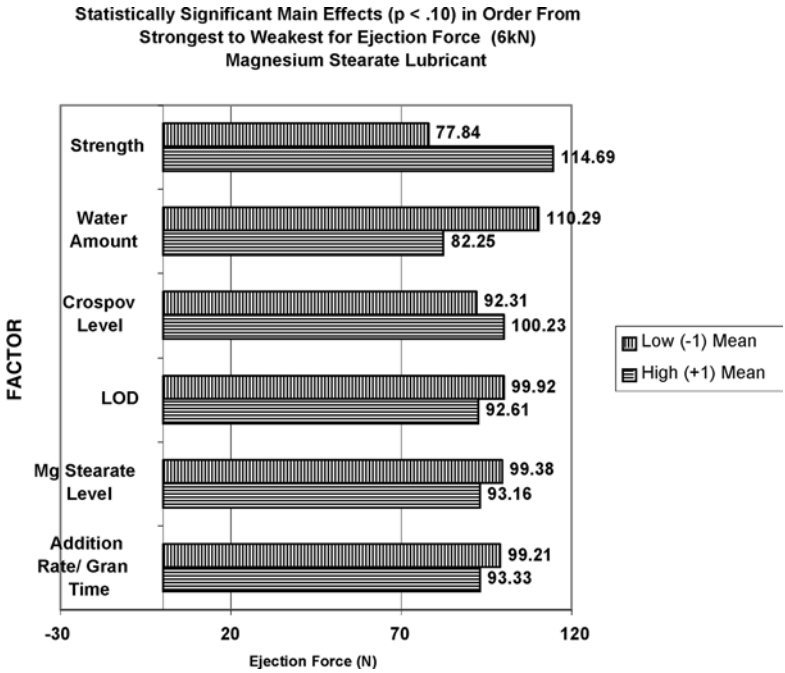

Figure 12 Factors affecting ejection force of a tableting mixture prepared by wet granulation.

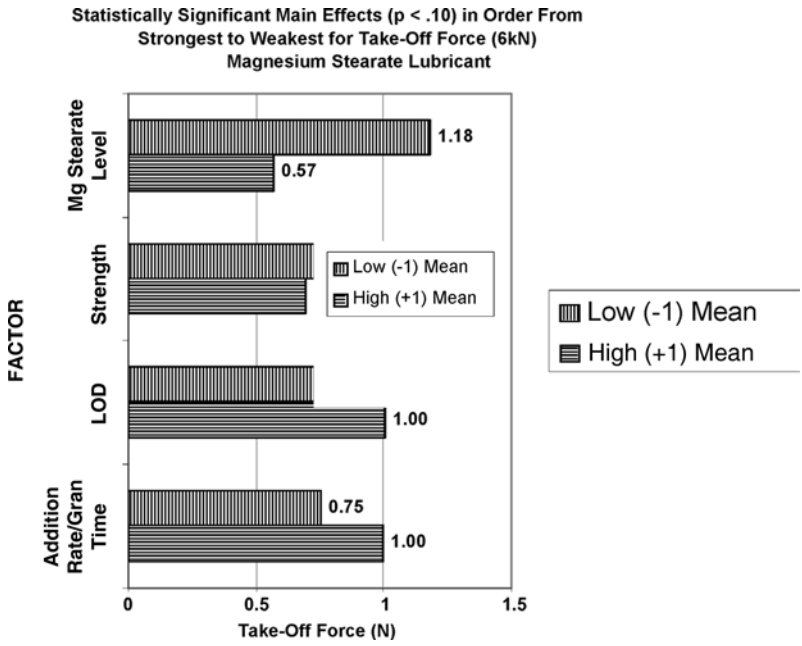

Figure 13 Factors affecting take-off force of a tableting mixture prepared by wet granulation can be selected.

Figure 14 shows the compression force monitored for an entire run, which lasted for 225 minutes. An average force of 18 kN was used to compress the batch. There were no significant fluctuations in forces observed throughout the run. This demonstrated satisfactory flow and minimal

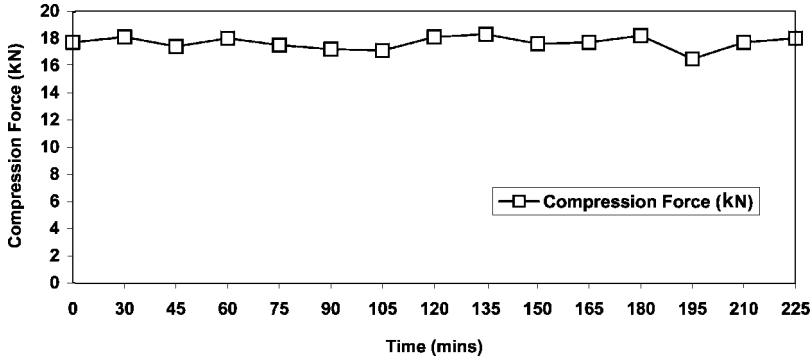

Figure 14 Compression force monitored over time.

Table 1 Tablet Physical Characterization Data

Sample	Average weight (min–max)	RSD (%)	Friability (%)	Disintegration time (minutes)
Start	619 mg (613–625)	0.6	0.36	3–5
Middle	619 mg (613–625)	0.6	0.30	3–4.5
End	618 mg (611–629)	0.8	0.34	3–4.5

weight variation. Table 1 shows the average weight at start, middle, and end of the compression run.

Another force measurement to monitor is the ejection force during the compression event. Figure 15 shows the ejection force monitored during the compression run. The ejection force was approximately 800 N throughout the compression run. This demonstrated that the blend was lubricated adequately. No picking/sticking was observed on the punch surfaces after 225 minutes.

SCALE-UP/VALIDATION

Scale-Up Process

In many companies, the scale-up process may include or overlap with the validation process. In any case, demonstration of the process in the production environment at full scale, using the materials, equipment, procedures, and personnel established in production, is required. Often, multidisciplinary teams are arranged to manage the scale-up, and the overall roles and responsibilities for those involved with the product may change. Typically, extensive documentation, including protocols and reports, is involved, as

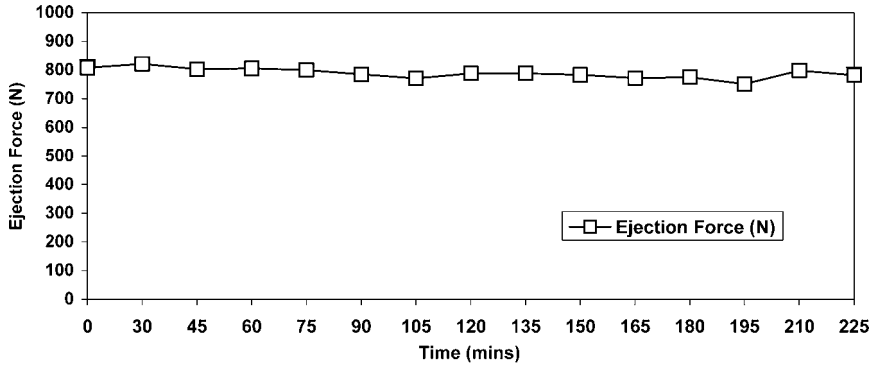

Figure 15 Ejection force monitored over time.

well as ancillary issues, such as cleaning assessments, material safety assessments, and transport tests. Timing is usually critical, since market launches may be forecasted at this time.

Equipment and Tooling

One piece of equipment that must not be overlooked is the tooling used for compression. To predict scale-up behavior of the tools, several approaches of increasing complexity can be utilized. At one end of the spectrum, an embossment/debossment that has some predictive properties for tablet picking or sticking can be used in development that will mimic the eventual brand logo. For instance, the number eight, with the two "islands" and curved embossment/debossments will challenge a formulation on its ability to pick. A more complicated strategy would be to define the number and size, including angles of the alphanumerics, for all tablet shapes and sizes, and then to use a representative alphanumeric sequence of the correct size and number to mimic the final commercial product.

Another consideration is the quality of the tools purchased from different manufacturers, where differences in the finish on the punch face may occur. Substantially different surfaces can be obtained from tools supplied by different vendors. Although this may not be noticeable to the naked eye, and the tools may meet specifications, a microscopic rough finish could lead to picking and/or sticking on the punch surface.

When scaling up to manufacturing facilities in the EU, one must consider the differences between TSM and EU tooling. The main difference between these two tools is the design of the punch head. This should be monitored carefully during scale-up, especially with products that are sensitive to changes in compression speeds and dwell times.

Specifications

Successful scale-up to a production environment may also be predicated on specific requirements established to increase efficiency during commercial manufacture. Based on existing equipment infrastructure within the production environment, and the experience base of the production management, many companies will use a decision tree to determine what process is more desirable as a first choice for a given tablet process, and which processes need to be avoided. For example, a company may prefer a direct compression process over a wet granulation process, since direct compression is more efficient than other tablet processes. Additionally, direct compression is easier to validate since there are less critical parameters involved. However, the direct compression process inherently carries a higher risk of failure, since it is more dependent on the quality of the drug substance and the consistency of the excipients used. Typically, these questions of suitable process are answered at a small scale, following the decision tree of preferable processes.

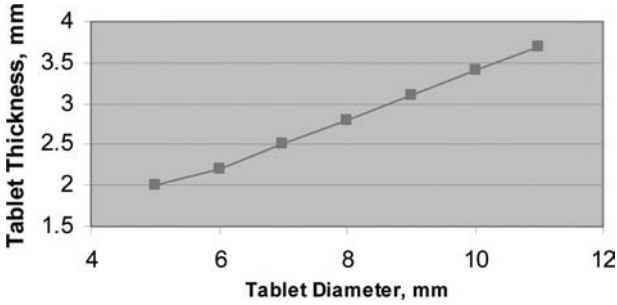

Figure 16 Preferred tablet thickness for flat-faced, round tablets based on production packaging tools.

In addition to the tablet process, the tablets themselves may be subjected to requirements to increase overall production efficiency. Round tablets may be preferred to other shaped tablets since the tools used to make round tablets rotate during compression, and, hence, they wear more uniformly. Also, production packaging requires specialized tools, and standardization of these packaging tools can be achieved by standardizing tablet shapes and sizes. For example, as shown in Figure 16, the size and thickness of round flat-faced tablets can be standardized to ensure that packaging tools for the tablets will be available. Also, the packaging validation required for the tablets should be less challenging, since similar size tablets have been validated on the packaging lines previously.

Predefined tablet sizes can be made for standard concave round tablets, as shown in Figure 17, or for non-round tablets, such as an oval shaped tablet, with geometric similarity.

Based on the same type of reasoning, i.e., packaging requirements and experience in the production environment, similar in-house criteria can be

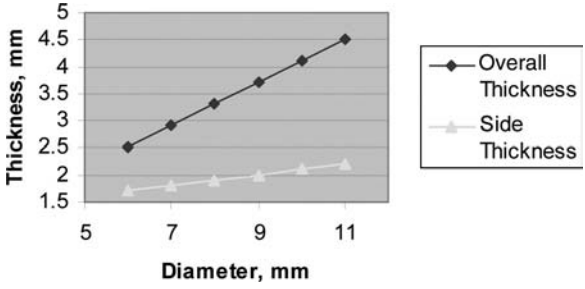

Figure 17 Preferred tablet thickness for standard concave, round tablets based on production packaging tools.

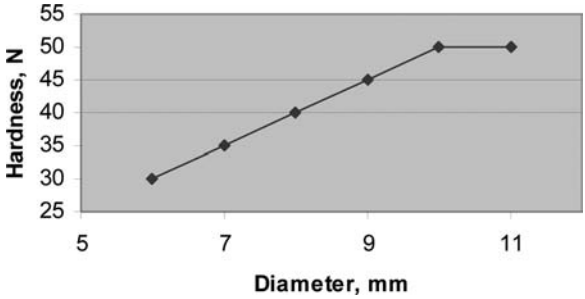

Figure 18 Minimum hardness values for round tablets based on production packaging tools.

set for the hardness of tablets. As shown in Figure 18, a minimum hardness for round tablets can be established that will ensure minimum breaking during packaging and shipping.

These guidelines can be extended to account for other tablet properties. For instance, based on experience gained in divisible tablets, a case can be made to restrict scoring of standard concave, round tablets to diameters of 9 mm and above, whereas flat-faced, round tablets can be successfully scored to diameters of 7 mm and larger.

The additional challenge to the tableting scale-up process will be to remain within these standardized ranges.

In-process guidelines during tableting are partly derived from internal experience and also from various regulatory agencies worldwide. Typically, in-house in-process guidelines are more restrictive than those of the regulatory agencies, since this will ensure a robust manufacturing process. As an example, the hypothetical guidelines shown in Table 2 could be established to control routine tablet production. Development of a tablet will need to be focused on the ability to meet these controls.

Troubleshooting

Through the use of predictive studies, compaction simulation and the investigation of critical tableting parameters at pilot scale, scale-up problems associated with the compaction operation should be minimized. Failure to achieve a required tablet hardness or the observation of insufficient lubrication of the mixture are preventable problems that suggest improvements in the development strategy. However, problems such as these can often be resolved through equipment and/or process changes. Most often, the use of precompression, changing the tablet position in the die during compaction, or altering the speed of compression can alleviate the problem. In these instances, one is actually mimicking the development environment in production.

Table 2 Hypothetical In-House In-Process Tableting Controls

Tablet weight	Action limit $N = 20$ ±(%)	Tolerance limit $N = 20$ ±(%)	
Average of 20			
<250 mg	2.0	4.0	
≥ 250 mg	1.5	3.0	
Individual weights	Action limit $N = 20$ ±(%)	Tolerance limit 18 of 20 ±(%)	20 of 20 ±(%)
<250 mg	7.5	7.5	15
≥ 250 mg	5	5.0	10
Friability	Maximum weight loss %	Maximum breakage number	
Unscored tablets			
125 revolutions		0	
400 revolutions	2.5		
<200 mg		2	
>200 mg		1	
Scored tablets and cores for film coating			
400 revolutions	1	0	
Film coated tablets			
125 revolutions	N/A	0	
<200 mg		2	
>200 mg		1	

Despite the diligent use of predictive studies, compaction simulation, pilot scale work, the state of the art of tablet scale-up still provide opportunities for problems to arise. The issues typically encountered are those that have multiple factors involved, and are difficult to predict and simulate at smaller scale. Of these problems, tablet mixture flow, including weight uniformity and segregation, and sticking and picking of the tablet mixture to the tools and tablet specks, are common occurrences.

Tableting mixture flow problems can occur on scale-up, since larger bins, longer holding times of intermediates, different ducting to the press, increased machine vibrations and higher number of dies requiring filling will be present in the production environment. The larger bin volumes and increased vibrations will allow more consolidation of the tableting mixture and often flow problems such as "rat-holing" will be observed. Also, the geometry of the mixture feed lines to the press allow increased opportunity for particle segregation. Finally, the length of time during a production

tableting run is usually much longer than during those studies in development and presents a longer time for films to form on the tools from the tableting mixtures, resulting in a sticking and/or picking problem. These problems may be amplified by the increase in temperature of the mixture during the longer time of a production tableting run.

Solutions to these issues are usually made through minor changes which are within the validated process. Such process changes include different feed arrangements (including the ultimate in scoop to hopper feeding), vibrators attached to locations throughout the feed lines, different press set-ups (cams, depth of die compression, and tapered dies), different styles of force feeders, tooling embossment/debossment angles, sizes, and location (upper or lower), and various finishes and/or polishes on the tools to prevent sticking. In some instances, for unknown reasons, the use of a different tablet press may be the difference required for a successful production tableting process.

CASE STUDIES

Scale-Up of a Wet Granulation Tableting Process

In this example, a high dose (~75% drug loading) wet granulated tablet product was transferred between development sites. The following issues were noted after transfer of the product:

- marketing decision to change from an uncoated tablet to a film coated tablet,
- high friability of the core tablet,
- change from a top-driven high shear granulation process at development center I to a bottom-driven high shear granulation process at development center II (at the request of the production site).

A 20 run 2^{5-1} fractional factorial design with four replicate center points was carried out to assess whether it was possible to optimize the current formulation for scale-up or if major reformation would be necessary. Table 3 lists the formulation variables that were evaluated.

Table 3 2^{5-1} Experimental Design, Formulation Variables and Their Ranges

Variables	−1 (%)	0 (%)	+1 (%)
Binder level	2	4	6
Disintegrant level	2	3	4
Lubricant level	0.5	1	1.5
Glidant level	0.1	0.3	0.5
Water level	20	22.5	25

Tablet hardness, friability, disintegration time and dissolution at 30 minutes were the response variables that were measured. Tablets manufactured at 10 and 12 kN were compared, as well as their compaction profiles. Table 4 shows the results from the fractional factorial DOE and Figure 19 shows the compaction profiles from the 20 batches.

The results indicated:

- tablet hardness was impacted by binder, disintegrant, and water levels,
- disintegration time was impacted by water, disintegrant, and lubricant levels,
- critical formulation variables influencing friability could not be determined due to the variability in the friability results,
- no impact on dissolution was observed—>80% of the drug substance was released within 30 minutes.

Two additional experimental designs were carried out to optimize the formulation and granulation process (water addition time, granulating time, and addition of binder—dry versus in-solution—binder level, disintegrant level, and lubricant level). There was a trend toward improved compaction profiles and reduced friability with increased granulation time. It was also observed that the lubricant and disintegrant levels affected the friability of the tablets. The effect of the lubricant level on tablet friability is shown in Figure 20. The final formulation and process are summarized in Table 5.

The blends with greater than 1% magnesium stearate had increased friability, and as the magnesium stearate levels increased, the disintegration time also increased. Magnesium stearate levels of 0.5% to 0.75% yielded similar friability results. Based on the fact that past experience in production indicated that coating processes would be successful with friability values <0.6%, and in attempting to keep the disintegration time under 10 minutes, 0.625% magnesium stearate was chosen as the target concentration.

Prior to scaling up to production, pilot batches were manufactured at the 40 kg scale. In order to show the robustness of the process at the pilot scale, the lubricant level, and the water level, as well as processing variables such as drying temperature, granulating time, and compaction force, were varied as shown in Table 6.

By showing robustness around these parameters, there is increased confidence that the formulation and process can be successfully scaled-up under target conditions for these parameters.

Figure 21 compares the compaction profiles from the 1 kg scale (at target conditions), 40 kg scale (plus and minus conditions) and 280 kg scale (at target conditions) batches.

Through the use of DOE, a robust formulation and process were developed, resulting in tablets that could be produced at production scale. The compaction profile shifted slightly on scale-up to production, but tablet

Table 4 Results of the 2^{5-1} Experimental Design

Run	Binder (%)	Lubricant (%)	Disintegrant (%)	Glidant (%)	Water (%)	Compression force (kN)					
						Hardness (Kp)		Disintegration time (secs)		Friability (%)	
						10	12	10	12	10	12
1	6	0.5	4	0.5	20	13.0	13.8	272	312	0.2	0.2
2	2	1.5	2	0.5	25	10.6	11.7	105	160	2.6	1.7
3	2	0.5	2	0.5	20	10.8	13.2	60	100	2.0	1.1
4	2	0.5	2	0.1	25	11.3	12.6	75	85	2.0	1.5
5	4	1	3	0.3	22.5	11.9	12.7	260	330	1.3	1.0
6	6	1.5	4	0.1	20	11.9	13.4	360	480	1.3	5.7
7	6	0.5	2	0.1	20	13.0	14.4	784	800	0.4	0.3
8	6	1.5	2	0.5	20	12.0	13.3	750	930	0.5	0.5
9	4	1	3	0.3	22.5	11.6	12.2	270	310	1.2	0.7
10	6	1.5	4	0.5	25	11.9	13.1	378	483	0.3	0.3
11	6	0.5	2	0.5	25	13.6	15.0	774	877	0.4	0.4
12	6	1.5	2	0.1	25	13.7	15.2	1034	1174	0.5	0.5
13	6	0.5	4	0.1	25	13.3	14.9	380	520	0.5	0.5
14	4	1	3	0.3	22.5	11.8	12.7	192	340	0.3	0.4
15	2	0.5	4	0.5	25	11.1	13.0	62	123	0.3	0.2
16	2	1.5	2	0.1	20	10.0	11.1	62	132	0.9	0.6
17	4	1	3	0.3	22.5	11.2	12.1	159	233	0.4	0.3
18	2	1.5	4	0.1	25	10.2	11.1	113	114	0.1	0.2
19	2	1.5	4	0.5	20	10.4	10.6	72	113	0.6	3.5
20	2	0.5	4	0.1	20	10.6	11.7	140	72	0.8	0.5

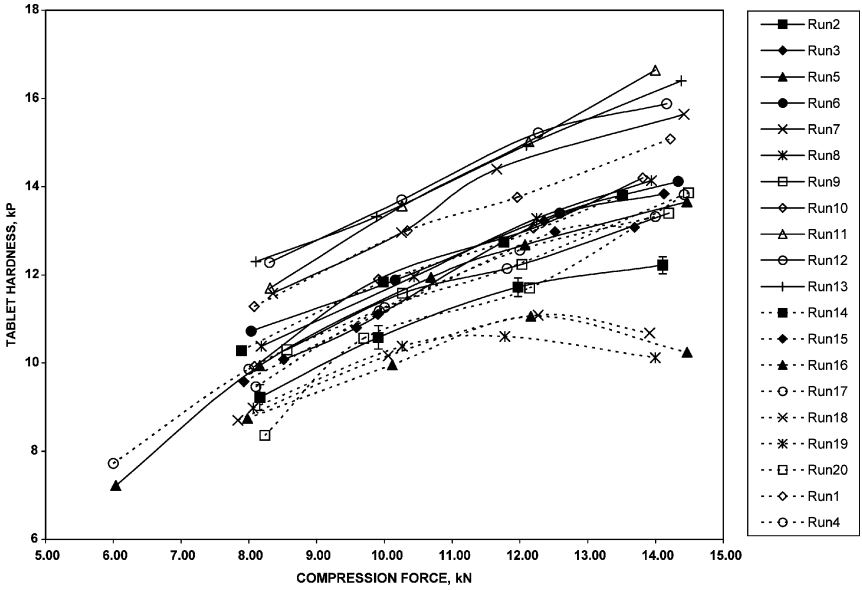

Figure 19 Compaction profiles from the 2^{5-1} experimental design.

hardness and friability were acceptable for coating within this range. Tablets with acceptable hardness and friability were manufactured over a specified force range and over the validated range of speeds for the production tablet press. This offers production flexibility, so that adjustments in force and speed

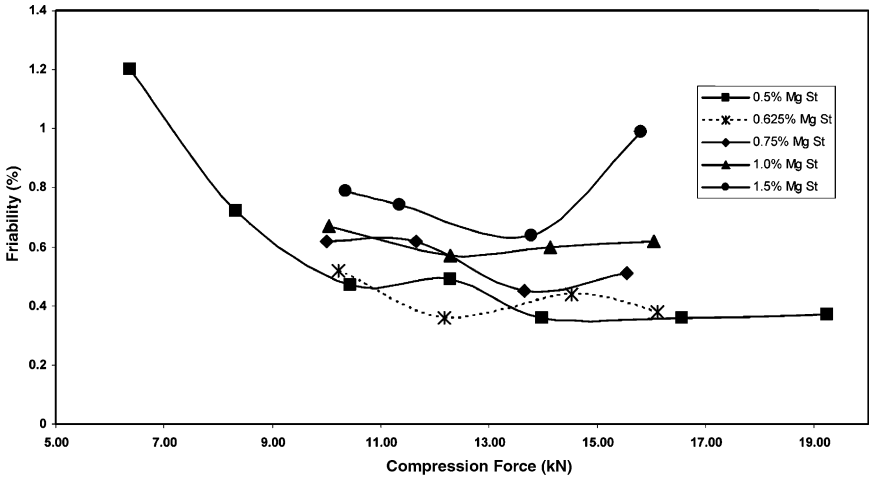

Figure 20 Effect of magnesium stearate level on tablet friability.

Table 5 Target Formulation and Process Condition

Variables	Target
Binder level	4%
Disintegrant level	4%
Lubricant level	0.625%
Glidant level	0.3%
Water level	22%
Water addition rate	3 min
Granulation time	6 min

can be made to accommodate batch-to-batch variability that might occur in the drug substance or raw materials used to manufacture the drug product.

Scale-Up of a Direct Compression Tableting Process

This compound was moisture-sensitive and could have potential incompatibilities with excipients in the presence of moisture. Hence, a direct compression process was used during development. Three strengths—25, 50, and 100 mg—were identified.

Using pilot trials, an evaluation was done on the compression force and speed for each strength. The compression force and speed evaluation indicated that tablets could be made with compression speeds ranging from 80,000 to 200,000 tph and compression forces of 4.8–12.6 kN (25 mg), 6.9–11.2 kN (50 mg), and 6.8–16.0 kN (100 mg). Acceptable IPC results were observed during the speed evaluation. The higher press speed range demonstrated robustness of the formulation and allowed production flexibility for higher product volume manufacture. The tablets from each strength made at high compression force had acceptable weight variation, friability, and disintegration time.

Figure 22 shows the tablet hardness profiles of the 25 mg strength. Tablet hardness slightly increased as the compression force increased and

Table 6 Pilot Scale Condtions

	Minus batch	Plus batch
Water level	20%	24%
Granulation time	4 min	8 min
Drying temperature	60°C	80°C
Lubricant level	0.5%	0.75%
Compaction force	Low	High
Compaction speed	High	Low

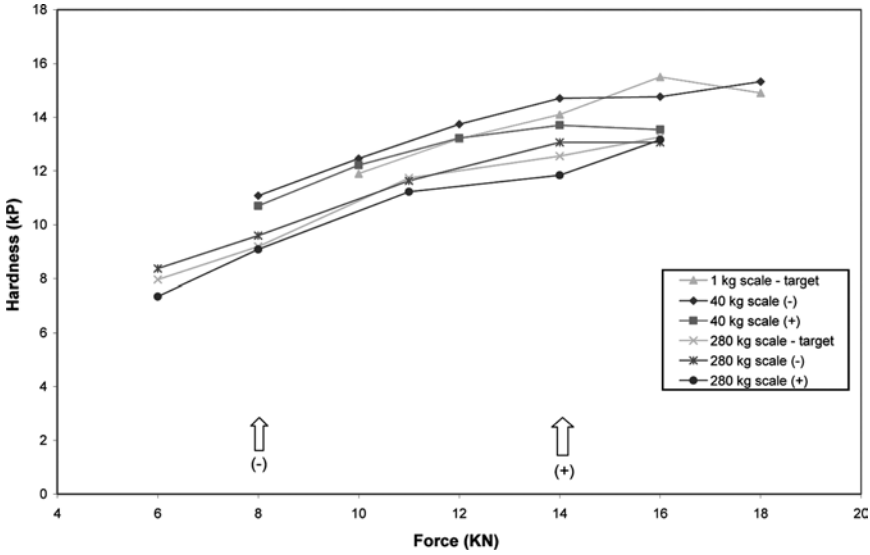

Figure 21 Scale effects for force versus hardness profiles.

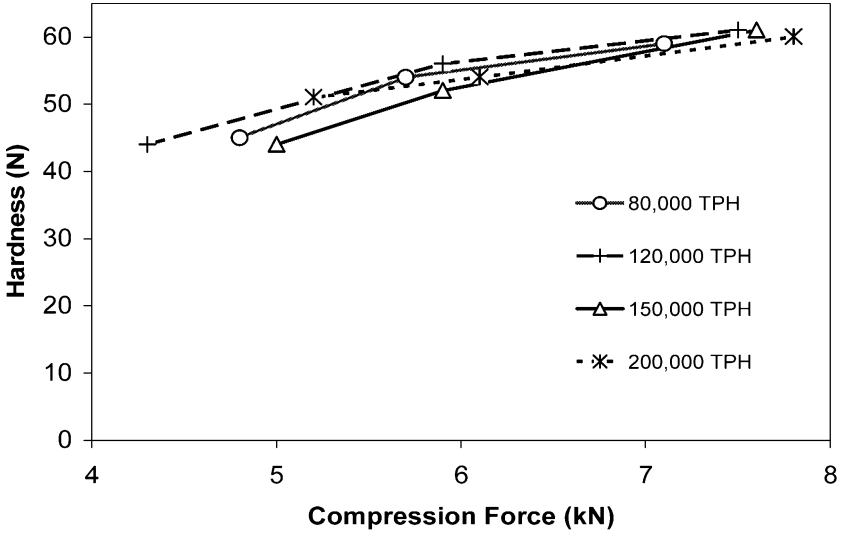

Figure 22 Compression curve for 25 mg strength tablets.

that press speed had no impact on tablet hardness. Tablet hardness profiles of the 25 mg strength were similar at compression ranging from 80,000 to 200,000 tph using a Fette 2090 tablet press with 43 stations. Therefore, based on the data, the target compression speed identified for 25 mg was 130,000 tph (range 80,000 to 180,000 tph). Average tablet hardness increased from 44 to 61 N at compression forces between 4.3 and 7.8 kN, with individual tablet hardness ranging between 35 and 70 N. Tablet friability results were a maximum of 0.1% (specification $\leq$1.0%). Tablet properties (friability, disintegration time, and thickness) were acceptable at compression forces up to 12.6 kN; the compression curve reached a plateau at a maximum tablet hardness of 67 N.

Similar observations were seen for the 50 and 100 mg strengths, where the press speed had no impact on tablet hardness. The data showed that the tablet hardness profiles were similar at compression speeds ranging from 80,000 to 200,000 tph. In process control, data such as friability, disintegration time, thickness, and hardness were all within set specifications.

Scale-Up of a Sustained Release, Wet Granulation Tableting Process

During development, variables in the granulation process were evaluated for their impact downstream during the compression process. These variables included granulating liquid level and binder level for their impact on particle size, compressibility and dissolution, and lubricant level for its impact on compressibility and dissolution. The responses evaluated during compression were tablet hardness (at different compression forces), weight variation, thickness, friability and dissolution. These variables resulted in process related problems. The low levels of granulating liquid yielded a finer particle size, which caused flow problems during compression. The high granulating liquid and binder levels gave larger particles which exhibited inferior compressibility. Friability for all variations was acceptable.

Granulation particle size did not impact the release rate. In addition, tableting at various compression forces had no significant impact on the release rate of the tablets. This knowledge that variability in tablet manufacture resulted in a uniform sustained release dosage form provided an advantage for further process optimization and scale-up, as shown in Figure 23.

Subsequent to these successful pilot scale trials, the formulation was scaled-up to the production launch site. Once again, only those parameters recognized as critical were modified during manufacture. The compression parameters that were modified were speed and hardness. A total of four production-sized batches were manufactured, with the first batch being compressed on a 43 station Fette 2080 rotary tablet press, and three subsequent batches compressed on a 36 station Fette 2090 rotary tablet press. Three compression speeds and three compression forces were successfully evaluated

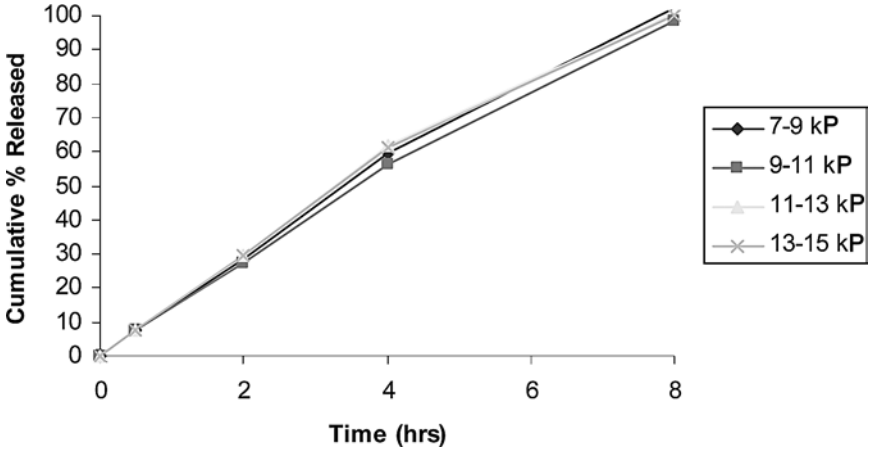

Figure 23 Effect of hardness on release rate.

during these batches. Due to the differences in size of the turret, the output of tablets per hour was kept constant, with the press speed adjusted within normal production operating ranges. For the first batch on the 2080, portions were compressed at the various compression conditions, whereas for the three subsequent 2090 batches, each batch was entirely compressed at the target conditions. The results can be seen in Tables 7 and 8.

For this sustained release tablet formulation, it was critical to match the dissolution profile in light of the changes in processing parameters. As shown below in Figure 24, the dissolution profiles at all speeds and hardness values were not significantly different.

By identifying critical process parameters early on in the development process, a robust formulation was developed and successfully scaled-up

Table 7 Compression Parameters for Scale-Up Batch 1

Compression force	Compression speed (tph)	Turret speed (rpm)	Average compression force (kN)
High	150,000	58	16.5
High	120,000	47	16.6
High	90,000	35	16.2
Target	150,000	58	10.8
Target	120,000	47	9.8
Target	90,000	35	10.0
Low	150,000	58	7.3
Low	120,000	47	7.0
Low	90,000	35	7.0

Table 8 Compression Parameters for Scale-Up Batches 2–4

Batch number	Compression speed (tph)	Turret speed (rpm)	Average compression force (kN)
2	90,000	41	14.7
3	120,000	55	11.1
4	150,000	69	10.0

which resulted in tablets that continue to meet specifications at production scale.

Scale-Up of a Dry Granulation Tableting Process

An advantage of roller compaction is the increase in bulk density resulting in a reduced tablet size. It can also be used to improve the content uniformity of low-dosage compounds. Characteristics which affect the tabletability of roller compacted formulas include over-lubrication and precompression of the compact. Typically, the powder is roller compacted between 15 and 40 kN of force prior to tablet compression.

Compression characteristics of roller compacted granulates are similar to direct compression powders. Force hardness profiles level off due to the limiting compaction of the precompressed granules. The compressibility of the compact is only as good as its last compaction run. Here, the same

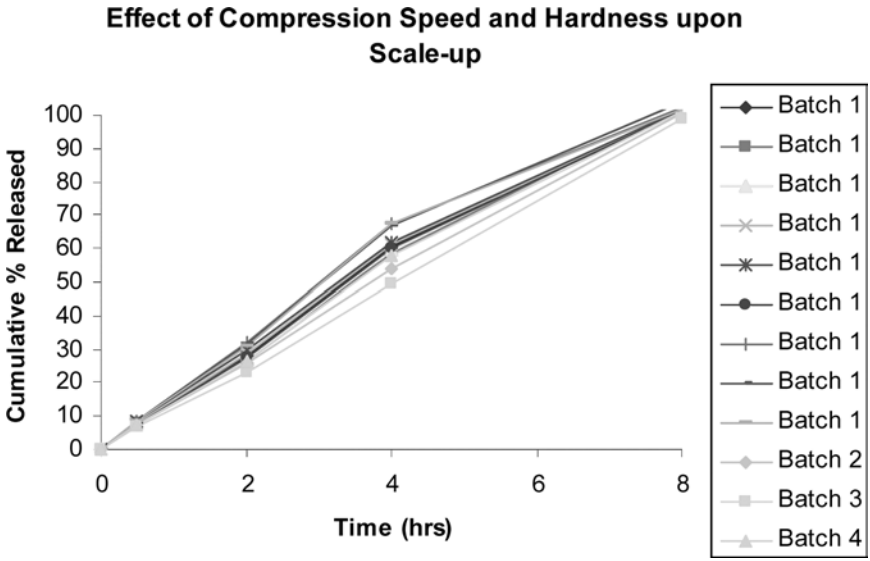

Figure 24 Dissolution data for batches 1–4.

formula was roller compacted at three different forces: 25, 30, and 35 kN. As expected, there is a rank order drop in the force hardness profile of the compressed cores as roller compaction force is increased, as shown in Figure 25.

Ejection forces are relatively higher for roller compaction tablets, although similar to direct compression. Ejection forces are usually 100–400 N, depending on the tablet weight and shape, as shown in Figure 26.

On scale-up to a high speed press at 120,000 tablets/hr, the roller compaction formulation is less predictable.

As shown in Figure 27, it is apparent that when the roller compaction force was scaled-up, the compactibility curve of the tablets shifted downward. Ideally, a formulator would prefer a 60 N hardness window of acceptable force. In this example, the flat part of the curve had no effect on friability and dissolution and thus could be processed. The example does show that for a roller compaction process, a scale-up factor must be considered for the roller compaction force early on in development. Factors that affect the tablet compactibility curve at scale-up include the roller compaction force and strain-rate sensitivity of the compact.

Scale-Up of a Bilayered Tableting Process

In addition to the scale-up issues mentioned in the previous case studies, there are scale-up issues specific to bilayered tablets. These specific issues include mixing of the granulation on the die table during compression,

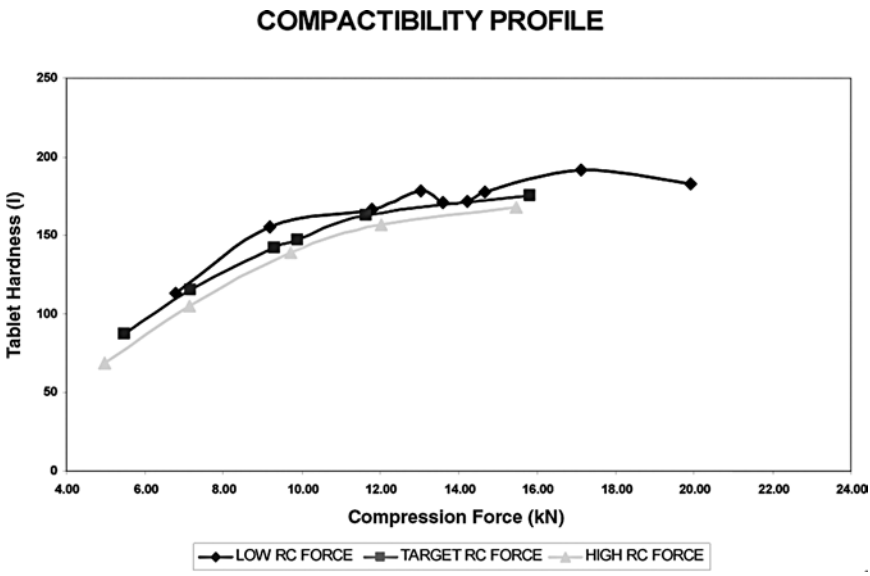

Figure 25 Compression profiles of tablet cores made from ribbons compacted at three different forces.

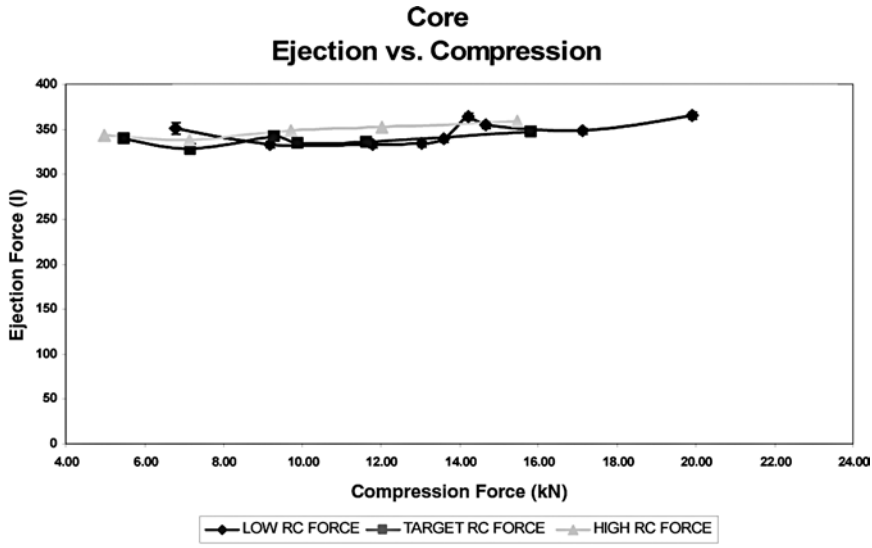

Figure 26 Ejection force profiles of tablet cores made from ribbons compacted at three different forces.

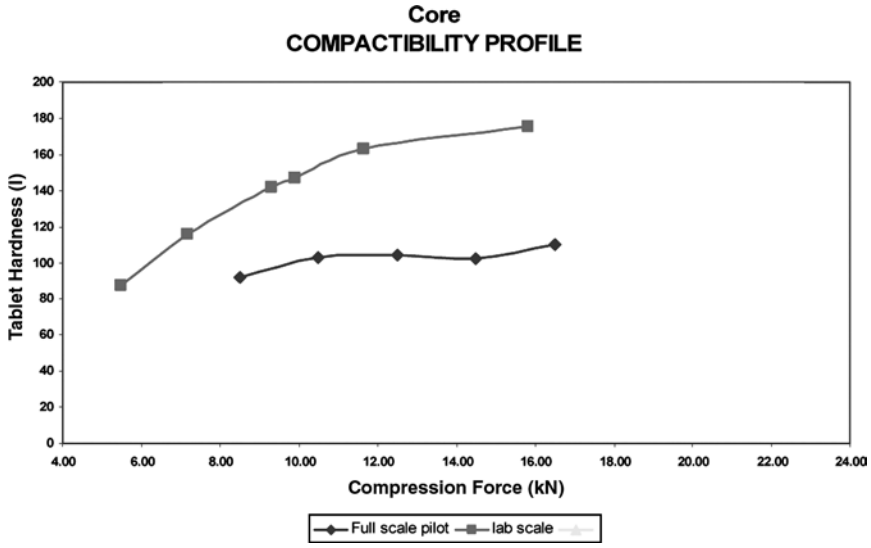

Figure 27 Compression profiles of tablet cores made from ribbons compacted at laboratory and production scale.

lamination of the bilayered tablets as a result of poor adhesion between the different components, limits on the ratio of first to second layer based on the overall standard deviation of the final bilayered tablet and the yield obtained from the tableting run. Although these issues can be encountered during development, they are exacerbated during scale-up, since several different mechanisms are used to achieved bilayered compression on various machines. Hence, it is unlikely that the same type of mechanism will be found on the development versus production machines. The mechanisms encountered to achieve bilayered compression could be as varied as the mechanical adaption of a two-sided press for bilayered compression, or as complicated as a bilayered press designed with mechanisms for obtaining the weight of the first layer as an in-process control during the tableting run. A case can be made for using a production press for development, based on the complexities involved, and often the type of development encountered for bilayered tablets allows large scale development activities, e.g., fixed combination line extensions to existing products.

Granulation mixing on the die table during bilayered tablet compression is dependent on the mechanisms of the press used to clean or feed back the first granulation prior to the introduction of the second granulation. Various zero tolerance feed frames, vacuum systems, and feed frame channels attempt to accomplish this on a production scale. It is the set up of the machine that will largely determine a successful separation. As a visual aid to scale-up and routine production, the addition of color to one of the layers is beneficial. The contrast in color between the layers allows the set-up operator to fine tune the machine setting to avoid excessive product mixing. Granulation mixing can result in other issues, such as stability or dissolution failures, which can become apparent during scale-up as the mixing is increased during scale-up.

The various attempts to minimize the granulation mixing on the die table results in losses that are larger than encountered for single layered tablets. As a scale-up issue, low yields are usually unacceptable in a production environment due to the costs associated with the waste. The yields typically encountered for a bilayered process are 90% or higher. Development approaches to improve the yield upon scale-up are those typical for a single-layer tablet, e.g., good granulation flow and absence of filming, sticking, or picking.

A key aspect of bilayered tablet development that aids scale-up is the ratio of the layered weights. The first layer is controlled directly during compression, as is the final tablet weight. However, the second layer is always obtained by the difference between the final tablet and first weight. This fact requires that the weight control of both the first and final weight must be excellent, since the standard deviation of the second layer is always higher, since it reflects the variations in both the first tablet layer and the total tablet weight control.

Table 9 Effect of First Layer Tablet Cylindrical Height on the Bilayer Core Tablets (8 mm Round Beveled Edge) Properties

Bilayer compression force (kN)	First-layer compression force (kN)	Tablet cylindrical height (mm)	Tablet hardness (N)	Tablet friability (% 500 Drops)
10.2	0.8	3.00	121.2 ± 5.7	0.28
10.0	1.0	3.00	127.5 ± 7.1	0.20
9.9	1.2	2.45	122.5 ± 5.3	0.10
9.7	1.4	2.15	119.6 ± 7.8	0.12

Bilayered tablets are more susceptible to lamination, either during compression (capping) or further downstream in processing, e.g., during tablet film coating and/or packaging. The increased tendency to laminate is a result of the reduction in bonding between the layers caused by the precompression of the first tablet layer. It has been shown by many studies that minimizing the tamping force used on the first layer will improve the overall tablet layer bonding. As shown in Table 9, increased tamping of the first layer resulted in a slight reduction in the overall hardness of the tablet.

The first-layer cylindrical height after tamping is inversely related to the tamping force. Therefore, minimizing this tamping force will decrease the amount of fill volume obtained for the second layer, and also increase the degree of mixing between the layers.

During scale-up of a bilayered tablet, it is necessary to determine the range of tamping that can be tolerated for a product. Typically, the tamping force and overall compression force are varied and the tendency to laminate is observed. In addition, the other tablet characteristics are also determined, e.g., hardness, thickness, weight uniformity, disintegration, and dissolution.

Due to the added complexity of the second layer, bilayered tablets may exhibit a strong dependence on the overall tablet size. As shown in Figures 28 and 29 below, changing the size of the tablet from 8 to 9 mm substantiality changed the resulting compression profile and friability properties of the tablet, respectively. This type of dependence on tablet size should be investigated before scale-up, since tablet designs often change during the scale-up and validation process.

As an example of the additional requirements posed by bilayered tablets during scale-up, a summary of the typical in-process tests is shown in Table 10.

PROCESS ANALYTICAL TECHNOLOGY

The recent FDA initiative on Process Analytical Technology (PAT) attempts to define a design space for unit operations such as compaction

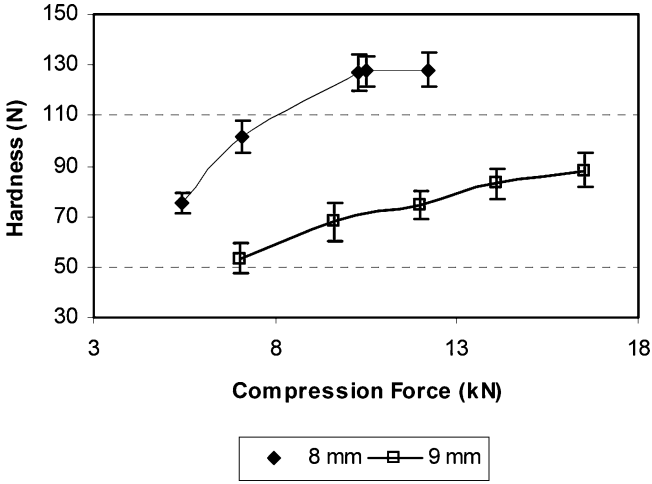

Figure 28 Dependence of the compression profiles of bilayered tablets on size.

where on-line monitoring of the process will allow in-process changes to control the product within established quality attributes. On-line adjustments of quality parameters as described by PAT may preclude the need for scale-up parameters, since the defined model may already be able to produce quality product from the processing parameters despite the manufacturing scale.

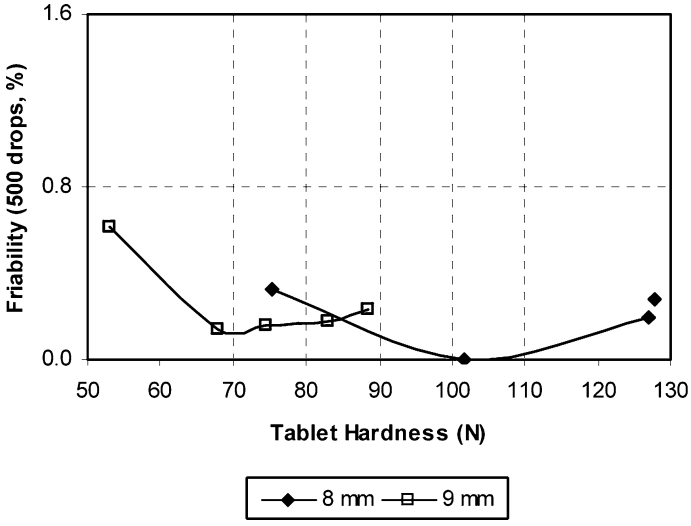

Figure 29 Dependence of bilayered tablet friability on size.

Table 10 Summary of IPC Tests for Bilayer Tablets

Parameters tested	Specifications
Average first-layer tablet weight ($n = 20$)	Action limit: ± 1.1% Tolerance limit: ± 1.7%
Individual first-layer tablet weight ($n = 20$)	Action limit: ± 2.0% Tolerance limit: ± 3.0%
Average bilayer-tablet weight ($n = 20$)	Action limit: ± 1.1% Tolerance limit: ± 1.7%
Individual bilayer-tablet weight ($n = 20$)	Action limit: ± 2.0% Tolerance limit: ± 3.0%
First layer-tablet cylindrical height	2.45–3.00 mm

More realistically, scale-up effects would have to be built into the model, or the model would have to be validated at a constant scale in production.

PAT is challenging the current approaches to the scale-up of tablet processes. For the tableting process, on-line, force-loop-feedback systems are used for weight control on most production tablet presses. Upper and lower punch forces, as well as mean punch force, can be monitored by load cells for each station on the tablet press. Deviations between the target and actual compaction forces are measured and adjustments to the punch filling depth are automatically made to bring the mean force back into the target range. In some cases, the speed of the force feeders on the press is adjusted by reducing the observed variability of the compression force data.

The Tandem™ system (Bruker Optics) is available for use during tablet production to measure tablet weight, thickness, hardness, and diameter, as well as online NIR content uniformity. The system can provide online analysis for drug substance uniformity, moisture content, and excipients. The advantage of systems like this is that the necessary data are available immediately to make adjustments to the production parameters in order to improve product uniformity. Therefore, adjustments can be made to tablet weight in real time in order to achieve 100% of the label claim.

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13

Practical Considerations in the Scale-Up of Powder-Filled Hard Shell Capsule Formulations

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INTRODUCTION

Hard shell capsules occupy a central role in drug product development and manufacture, ranking second behind compressed tablets in frequency of utilization in drug delivery. In product development, such capsules are often the first dosage form for any orally administered drug substance. Although the expectation may be that the final marketed form will be a compressed tablet, firms may consider using the capsule as the first marketed form to shorten the overall development cycle.

Most drug substances are provided to the formulator in the form of dry, particulate solids, and the initial development goal typically is to produce an immediate release oral solid dosage form. Preformulation studies will determine whether a drug substance can be filled in the form of relatively simple powder blends or must be granulated. Although hard shell capsules may be filled with a range of materials other than powders and granulations, such as pellets, semi-solid matrices, and tablets, and even combinations of these, to provide modified release or, perhaps, to solve special formulation problems related to poor drug solubility or compatibility, the scope of this chapter will be limited to capsules filled with simple powder blends or

granulated powders. This chapter will not discuss the issues of scaling-up of blending or granulation. These unit operations are not exclusive to capsules and are treated elsewhere in this book. Similarly, the scale-up issues related to tablet compression, coating pellets, and coating tablets are also discussed elsewhere. Rather, this chapter will address the issues involved in transferring simple powder blends or granulated powders from a smaller capacity filling machine to a larger capacity filling machine.

TYPES OF FILLING MACHINES AND THEIR FORMULATION REQUIREMENTS

The most common scale-up problems are related to bulk density, powder flow, compactibility, and lubricant distribution. Therefore, any discussion of the issues of scaling-up capsule filling must take into account the design and operating principles of filling machines and their formulation requirements.

Most production capsules are filled on machines that form plugs by compression with tamping pins or pistons in a manner somewhat analogous to the action of tablet punches, and then eject the plugs into capsule bodies. Although the compression/ejection events bring to mind tableting, it is important to recognize that capsule plugs are vastly different from compressed tablets. In the first place, plug height to diameter ratios are typically >1 and often as high as 5:1. This is in marked contrast to tablets, where the height to diameter ratio is generally <1. Furthermore, plug compression forces, often in the range of 50–200 N, are about 50–100-fold less than typical tablet compression forces. The resulting plugs are very soft, and when they can be handled, they often exhibit breaking strengths of less than 1N (1). However, plugs need only retain their mechanical integrity until delivered into the capsule body and often are not recovered intact from the filled capsule. Interestingly, relatively high piston or tamping pin compression speeds in the range of about 100–500 mm/sec have been reported for several machines (2–4). These rates easily exceed the approximately 50 mm/sec range considered typical of traditional single-station eccentric tablet presses (5) and bracket the maximum total punch speed of about 250 mm/sec reported for the double-ended compression event of a Manesty Betapres operating at 1300 tablets/min (6). Finally, as will be discussed below, unlike the formation of many tablets, plug forming machines do not necessarily form plugs with a single compressive stroke.

There are two main types of plug forming machines: the dosator type (e.g., MG2, Zanasi, and Matic machines) and the dosing disc type (e.g., Bosch GKF, Impressa, and Index machines). Bosch GKF machines were formerly manufactured by Höfliger and Karg (H&K). Both types of machines have capsule rectification and separation operations in common. As empty capsules are fed into these machines, they are first rectified, i.e., oriented so that they are delivered body-end down into split bushings.

Separation occurs when an applied vacuum pulls the body segments down into the lower portion of the split bushing, leaving the cap segment behind in the upper bushing portion. When the split bushings are separated, the capsule bodies are exposed for filling with plugs.

The two types of filling machines form plugs by different mechanisms. Ideally, the type of machine chosen for routine production should dictate the properties of the formulation to be filled.

Dosator Machines

One type of machine employs a dosator. The dosator can be viewed as a hollow tube containing a moveable piston (Fig. 1). The piston is preset to a particular height in the tube so that the volume between the piston head and the open end of the dosator would contain the appropriate mass of the formulation. In operation, the open end of the dosator is plunged downward into a powder bed that had been struck-off neatly at a particular height.

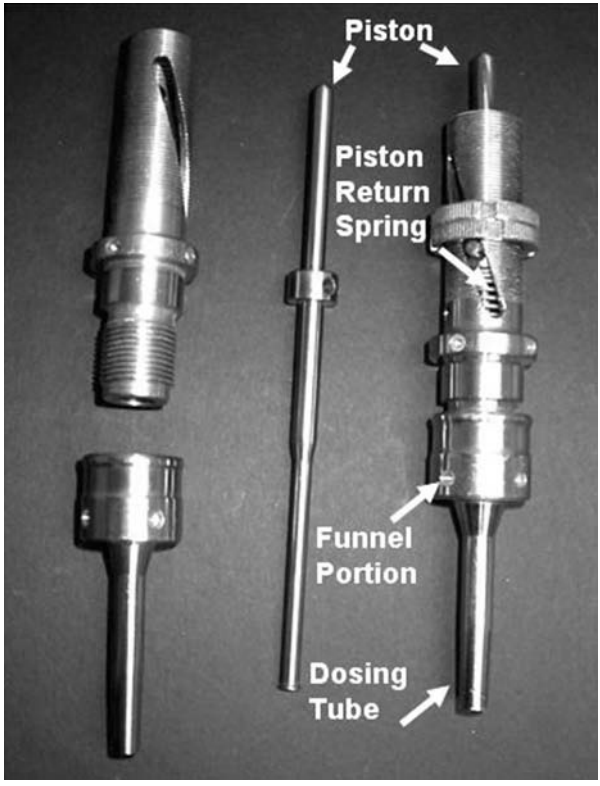

Figure 1 Dosator from a Zanasi LZ-64 intermittant motion filling machine.

Often, the powder bed height is as much as double the piston height. Thus, as the dosator moves down through the powder bed, the formulation enters the open end of the dosator and becomes lightly compressed against the stationary piston. While the dosator is in its lowest position in the powder bed, these machines can provide additional compression to the plug via the piston through a compression knob or cam mechanism. When plug compression is complete, the dosator and plug is lifted out of the powder bed and positioned over an open capsule body segment held in a bushing. The dosator piston is then depressed via an ejection knob or cam mechanism to push the plug from the dosator to the capsule body. In certain machines, the body bushing is rotated into position under the dosator to receive the ejected plug. Plug porosity and mechanical strength (breaking force) depend on the compression force. Plug weight depends on the piston height setting (primarily) and the powder bed height.

A successful filling operation with these machines requires the quantitative retention of powder within the dosator during transfer from the powder bed to the capsule shell. As a minimum, a stable powder arch needs to be formed at the dosator outlet to prevent loss of material during the time that the open end of the dosator tube is exposed (7,8). This stable arch is dependent on the angle of wall friction of the powder with the dosing tube and the degree of compression applied. An optimum angle of wall friction exists for which the compression force required to ensure a stable arch is a minimum (8). Quantitative transfer also requires that the plug ideally remain intact during the actual ejection event to prevent material loss. Loose powder can be lost with the displaced air. Formulations thus require cohesiveness, and fillers that have been modified to enhance both their flowability and compactibility may be particularly advantageous. These include, for example, microcrystalline cellulose, compressible (pregelatinized) starch, and various direct compression grades of lactose. Direct-fill powder formulations for dosator machines may benefit from the higher compactibility of cellulose-based compressibile fillers. Patel and Podceck (9) noted that medium and coarse particle size grades of microcrystalline cellulose can be considered "good" excipients for capsules based on studies using a Zanasi AZ5 dosator machine. Guo and Augsburger (10) demonstrated the higher compactibility of microcrystalline cellulose and silicified microcrystalline cellulose compared to Starch 1500 and anhydrous lactose at low plug compression forces.

Meeting a flowability criterion appropriate to these machines is also an important determinant of successful filling. Flowability is not only important for proper powder feed from the reservoir to the dipping bed, but also to facilitate the efficient closing in of the hole left by the dosator and reestablishment of the bed packing density before another plug is formed from that region of the bed. Dosator machines provide various agitation and scraping mechanisms to restore the powder bed, but proper flowability is nevertheless

required. Maintaining a uniform bed density helps assure that plugs of uniform weight will be picked up by the dosator and that plugs of uniform cohesiveness will be formed for a given compression setting. Irwin et al. (11) found that the better the rate of flow in a flow meter, the more uniform the capsule fill weight on a Zanasi LZ-64 machine. Heda (12) found that powders exhibiting a Carr Compressibility Index (CI%) (13)[a] between 25 and 35 yielded minimum weight variation in a Zanasi LZ-64. Stronger plugs with lower weight variation were produced with higher CI% values (>30). Powders with CI% values <20 were more difficult to retain in the dosator tube. Very free flowing powders may tend to "flood" in the powder handling mechanism of a dosator machine.

Glidants (e.g., colloidal silicon dioxide, talc) may need to be added to achieve desired flow properties, especially when the drug/filler ratio is relatively high. Usually, there is an optimum concentration of glidant for best flow, often less than l% for the colloidal silicas (14,15). The following order of effectiveness of glidants has been reported for two powder systems: fine silica > magnesium stearate > purified talc (16).

Formulations typically also require the inclusion of a lubricant for successful filling. Lubricants reduce adhesion to piston faces and other metal surfaces with which the powder comes into contact, reduce friction between sliding surfaces, and ease the ejection of plugs. The same lubricants used in tableting are used in capsule formulations. The most commonly used lubricant is magnesium stearate, which also exhibits glidant activity. Comparing different concentrations of magnesium stearate in standard fillers in an instrumented Zanasi LZ-64 machine, Small and Augsburger (17) found minimum ejection forces at 0.l% magnesium stearate with pregelatinized starch, 0.5% with microcrystalline cellulose, and at 1% with anhydrous lactose. Moreover, the magnitude of the ejection force depended on the setting of certain operating variables. Generally, ejection force increased with compression force, but at a given compression force, ejection force also increased with increases in either the piston height or the powder bed height (Fig. 2). Based on an experimental design, Tattawasart and Armstrong (18) concluded that 0.5% magnesium stearate was optimal for α-monohydrate lactose when tested in a simulator for a Macofar 13/2 machine.

Dosing Disc Machines

In contrast to dosator machines, dosing disc machines form plugs in segments through a series of tamping or compression events. The dosing disc machines made by various manufacturers can vary in the number of

[a] The Carr Compressibility Index (CI%) is calculated from the loose (ρ_{Loose}) and tapped (ρ_{Tapped}) bulk densities as follows: $CI\% = \frac{\rho_{Tapped} - \rho_{Loose}}{\rho_{Tapped}} \times 100$ (13).

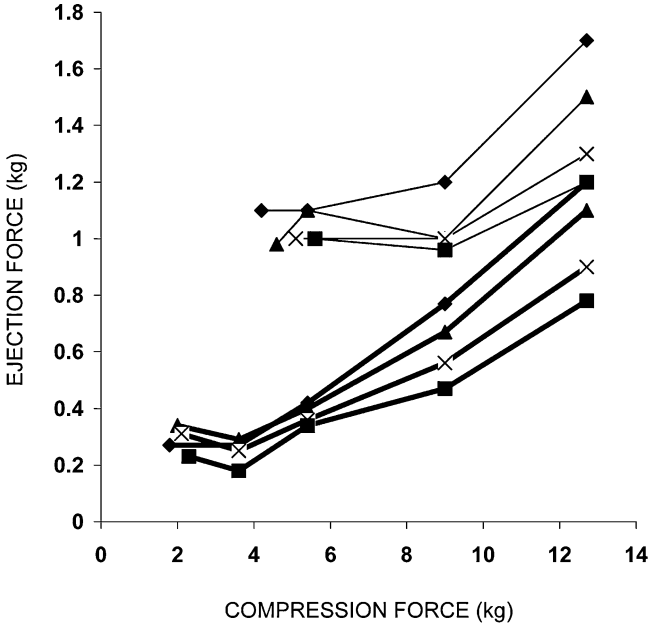

Figure 2 Effect of compression force, piston height setting and powder bed height on plug ejection force of Starch 1500® (0.005% magnesium stearate) on a Zanasi LZ-64 filling machine. *Source*: Redrawn from Ref. 17. *Key*: Piston height (mm): ◆, 15; ▲, 14; ×, 13; ■, 12. Powder bed height (mm): —30; –50.

tamping stations utilized and, in certain cases, may employ modified tamping mechanisms.

The plug-forming portion of dosing disc machines may be viewed as a powder bowl, the bottom of which is a plate through which sets of circular holes or perforations have been drilled (the "dosing disc"). The dosing disc rotates on a sealing plate that effectively closes off the sets of perforations to form the dosing disc cavities in which the plugs are formed. The dosing disc selected depends on the capsule size (determines the dosing disc cavity diameter) and the plug length that can be achieved for the required weight of a given formulation (determines the required disc thickness). The appropriate disc thickness for a given formulation can be estimated using a plug compression tester developed by Höfliger and Karg in which a dose of the formulation is compressed in a die with a single stroke and the plug length is measured (19). Davar et al. (20) suggested equations and a spreadsheet for predicting the required disc thickness based on the formulation density, and the length and breaking strength of trial plugs made using an Instron tester. However, a dosing disc whose thickness is adjustable is now available from Bosch for at least some models.

In GKF machines, sets of dosing disc cavities are arranged in equally spaced locations around the periphery of the dosing disc. Five of these locations serve as plug tamping stations, and the sixth is the plug ejection station (Fig. 3). Depending on the filling capacity of the machine, there may be as many as 18 dosing disc cavities at each location. The powder formulation is maintained at a relatively constant level over the dosing disc. The powder level is sensed by a capacitance probe and an auger feed mechanism is activated if the powder level falls below that of the sensor. Groups of tamping pins descend at each station to tamp the powder in the cavities to form plug segments. Plug segments are actually a composite of powder that enters the dosing disc cavities during disc rotation and any additional powder that enters the cavities during tamping as the pins push through the powder bed over the dosing disc (21). Most powder enters the dosing cavities by the former process (22,23). The cavities are indexed under each of the five sets of tamping pins where additional plug segments are formed, thus each plug is the result of five tamping events per cycle. In some applications, fewer than five tamping stations may be utilized. Shah et al. (21) reported that target fill weights could be obtained using a few as three tamping stations when filling certain lubricated fillers (Fig. 4). Excess

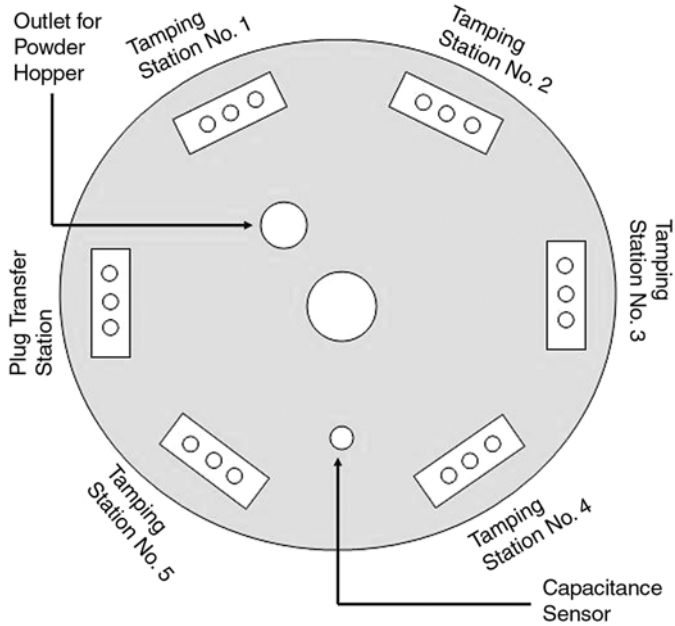

Figure 3 Diagrammatic representation of the disc area layout of a dosing disc machine (3 tamping pins per station).

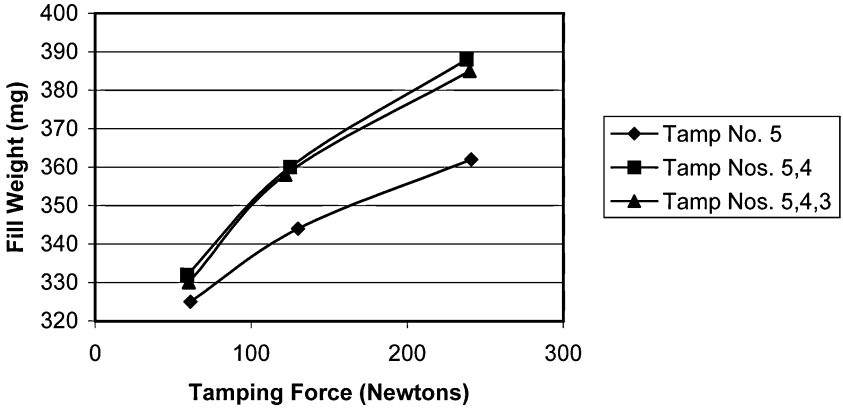

Figure 4 Effect of tamping force and number of tamps on fill weight in a Höfliger and Karg GKF 330 filling machine. Anhydrous lactose lubricated with 0.5% magnesium stearate. *Source*: Adapted from Ref. 21.

powder is scraped off as the dosing disc indexes the completed plugs to the sixth station where the bottoms of the dosing disc cavities are exposed and the plugs are ejected into capsule bodies held in a bushing by another set of pins (the "transfer pins"). In general, the dose delivered depends on the thickness of the dosing disc (i.e., cavity depth), the powder depth, the tamping pin penetration setting and the number of tamping stations used, if less than all five.

The tamping pin block of a Harro Höfliger Model KFM/3 dosing disc machine that utilizes three tamping pins in each of three tamping stations is illustrated in Figure 5. In this machine, the powder in the dosing cavities is tamped twice before rotating a quarter turn to the next station.

It is easy to see from the above description how pin penetration setting or compression force contributes to fill weight. Clearly, the greater the compression at any station, the larger will be the potential volume remaining to capture powder upon rotation to the next station. At the same time, the greater the tamping pin penetration distance, the more likely powder over the disc will be pushed into the dosing disc cavity. However, it is important to recognize that the pin penetration setting is not necessarily the actual penetration distance, since overload springs at the distal end of each pin compress when sufficient resistance is encountered due to the forming plug. Springs made from larger diameter wire make possible the development of higher compression forces which favor the attainment of greater fill weights (2).

A successful filling operation with these machines requires formulation attributes similar to those of dosator machines. Formulations require cohesiveness, and fillers that have been modified to enhance both their

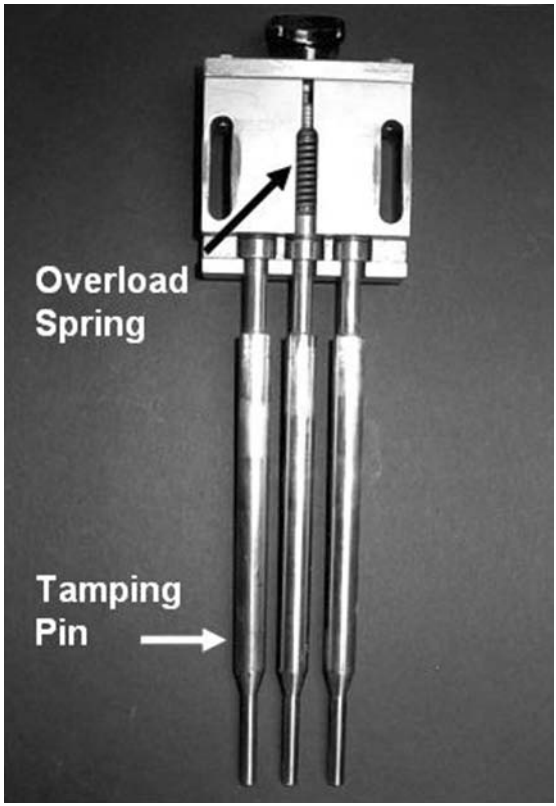

Figure 5 Tamping block and pins from a Harro Höfliger KFM/3 dosing disc machine.

flowability and compactibility are also likely to be advantageous. The same fillers used in dosator formulations are also used in dosing disc formulations. Meeting a flowability criterion appropriate to dosing disc machines is also an important determinant of successful filling. As with dosator machines, fillers may be selected for their flowability and an optimum concentration of glidant may be required. The same glidants and lubricants are used. Lubricants play the same role in dosing disc machines as they do in dosator machines. However, formulations that run successfully on dosator and dosing disc machines may differ in flowability, compactibility and lubricity, and these differences may need to be considered when transferring a formulation from one type of machine to the other. The differences in the formulation requirements of these two types of machines and their possible implications will be discussed in greater detail in the sections below.

Continuous Motion vs. Intermittent Motion Machines

Some machines, e.g., Bosch GKF, Index, Impressa and Zanasi, are called intermittent motion machines because they exhibit an interrupted filling sequence. That is, indexing turntables must stop at specific stations to execute the various operations described above. Continuous motion machines, e.g., MG2 and Matic, execute these functions in a continuous cycle. Eliminating the need to decelerate and accelerate from one station to the next makes possible higher machine speeds with the continuous motion machines (24).

GENERAL FORMULATION PRINCIPLES

The development of powder formulations for hard shell capsules can present formulators with significant challenges. Just as is the case in formulations for tableting, such problems as component compatibility, powder blending and maintenance of homogeneity, flowability and lubrication are frequently encountered. The ability to measure out and transfer accurate and precise volumes of a powder or granular mass to capsule shells is the determining factor in weight variation and, to the extent that mixing is uniform, also of content uniformity. As discussed above, consideration must be given to the proper choice and use of fillers, glidants and lubricants. Formulations must not only be designed to run successfully, but the capsule product must also exhibit appropriate drug release characteristics. Because some properties important to successful running also can adversely affect drug release, and vice versa, the interplay of formulation and process variables must be carefully considered in order to meet both objectives. For example, to improve their dissolution rate, poorly soluble drugs are often micronized as this increases their specific surface area (surface area per unit weight). Micronization is thus expected to speed up dissolution by increasing the surface area from which dissolution can occur. However, since micronized particles have high surface-to-mass ratios, surface cohesive interactions may enhance the tendency of such particles to aggregate, thus resulting in a smaller than expected effective surface area from which dissolution can occur. In one example of this phenomenon, larger particle size fractions of the poorly soluble drug, ethinamate, actually gave better dissolution from capsules of the neat drug than did smaller particle sizes when filled at equivalent porosities (25). The greater surface cohesive and frictional interactions of smaller particles also reduce their flowability.

For best drug release, it may be important to consider both the solubility of the filler and the drug. For instance, Newton et al. (26) long ago demonstrated that the dissolution of poorly soluble ethinamate from

capsules markedly improved when the lactose in the formulation was increased to 50%. Interestingly, with the soluble drug chloramphenicol, little or no effect on dissolution was found when the formulation included up to 50% lactose, but the inclusion of 80% lactose in the same formulation markedly retarded drug dissolution from the capsules, possibly due to competition for the solvent (27).

Good running formulations generally require lubrication; however, the most effective and most commonly used lubricants are such hydrophobic substances as magnesium or calcium stearate. Indeed, magnesium stearate is the most commonly used lubricant (28,29). The level of lubricant is critical. Excessive concentrations of hydrophobic lubricants have long been known to retard drug release from capsules by making formulations more hydrophobic (26,30). Laminar lubricants like magnesium or calcium stearate shear readily and delaminate when subjected to a tangential force in the blender (31–33). Thus, if a formulation is mixed for too long a period of time after the addition of such lubricants, the net result can be the formation of an excessive hydrophobic film on particle surfaces that resists wetting, thus retarding liquid penetration into the plug matrix, deaggregation of the matrix, and drug dissolution. Even a modest level of laminar lubricant can retard wetting and dissolution if the lubricant blending time is too long (34).

The presence of magnesium stearate at particle surfaces can also reduce cohesiveness and soften plugs. Mehta and Augsburger (1) found that the mechanical strength of plugs produced in a dosator can be reduced by the amount of lubricant used and that drug dissolution could benefit in certain cases. In a simple formulation consisting of hydrochlorothiazide, microcrystalline cellulose and magnesium stearate, plug breaking force decreased from 84 g to about 2 g and T_{60} decreased from 55 minutes to 12 minutes when the magnesium stearate level was increased from 0.05% to 0.75%. The capsules were filled on an instrumented Zanasi LZ-64 dosator machine using a constant plug compression force of 22 kg ($\sim$215 N). However, this phenomenon was not found when the filler was changed to anhydrous lactose. A similar phenomenon was previously reported for hand-filled rifampicin capsules (35). In that case, increases in the blending time of magnesium stearate, up to a limit, led to increases in the dissolution rate, and the effect was most pronounced at lower lubricant levels. The enhanced dissolution rate appeared related to a reduced cohesiveness of the formulation that resulted from increased lubricant mixing time (35). Aside from its possible effects on drug dissolution, over-lubrication, whether by over-mixing or adding excessive concentrations, could lead to increased weight variation in dosator machines because of its softening effect on plugs and/or by reducing dosing tube wall friction.

Other excipients that may appear in capsule formulations are disintegrants, and wetting agents. At appropriate concentrations in the

formulation, often 4–8%, super disintegrants, such as croscarmellose sodium, sodium starch glycolate and crospovidone, can enhance drug dissolution rate by promoting liquid penetration and capsule content dispersion or disintegration (36). This improvement in dissolution rate was much less marked when the low dose drug was formulated using lactose as the filler, as compared to water insoluble dicalcium phosphate (37). The lactose-based formulation was already a rapidly releasing system, and the soluble filler may tend to dissolve, rather than disintegrate. Of possible relevance to scale-up and/or transfer across filling machine types, was the observation that the beneficial effect of disintegrants was to a degree dependent on plug compression force, with dissolution tending to be enhanced at higher plug compression forces (37). Again, the effect was more apparent when the filler was dicalcium phosphate, as compared to the lactose-based formulation.

Capsule formulations may include wetting agents, such as sodium docusate and sodium lauryl sulfate. Typically used in concentrations of 0.1–0.5% and 1–2%, respectively, these excipients can help plug dispersion and drug dissolution by increasing the wettability and liquid penetration of the powder mass (25,26,38). Wetting agents can help overcome the "water-shedding" nature of hydrophobic lubricants.

Expert systems and artificial neural networks have been developed to help formulators develop successful formulations for hard gelatin capsules (39–41).

ROLE OF INSTRUMENTED FILLING MACHINES AND SIMULATION

It is apparent from the foregoing sections that the successful running of hard shell capsule formulations and the drug release properties of the filled capsules are dependent on a number of formulation and processing factors and their interactions. The formulator's understanding of how the interplay of these variables affects manufacturability and drug dissolution has been enhanced by the research instrumentation of automatic capsule filling machines to measure the forces involved in plug formation and ejection (42). Both dosator machines (43–47) and dosing disc machines (48,2,22) have been successfully instrumented. The development of instrumented capsule filling machines has also led to capsule filling machine simulation (3–4,49–51). The simulation of capsule filling is not nearly as well established as compaction simulation for tableting. Further development of this technology ultimately may permit the study of plug formation and ejection in the laboratory with only small quantities of material on equipment that can be programmed to simulate the action of different production machines at their operating speeds.

SCALING-UP WITHIN THE SAME DESIGN AND OPERATING PRINCIPLE

Regulatory Meaning of Same Design and Operating Principle

Generally, few problems are expected when scaling-up with equipment of the same design and operating principle. Indeed, the regulatory guidance on scale-up of immediate release oral solid dosage forms (SUPAC IR) (52)[b] appears to recognize this point. According to SUPAC IR, scale-up to and including a factor of 10 times the size of the pilot/biobatch is considered a Level-1 change if the equipment used to produce the test batch(es) is of the same design and operating principle, Current Good Manufacturing Procedures are followed, and the same standard operating procedures (SOPs), controls, and formulation and manufacturing procedures are used. Level 1 changes are those that are not likely to cause any detectable impact on formulation quality or performance and need only be reported in the annual report. Scale-up beyond 10 times the pilot/biobatch is only a Level-2 change, provided the equipment used to produce the test batch(es) is of the same design and operating principle. Similarly, the same standard operating procedures (SOPs), controls, and formulation and manufacturing procedures must be used. Level-2 changes are changes that could significantly impact formulation quality and performance and require the filing of a "Changes being effected supplement." It is significant that in neither case are in vivo bioequivalence data required to support the change of scale. The guidance should be consulted for a full description of the test documentation needed to be reported to FDA in these cases.

What constitutes equipment of the "same design and operating principle" was clarified in the recommendations of subsequent guidances. The current guidance, "SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum" (53),[c] applies to both immediate and modified release[d] oral solid dosage forms, was developed by FDA with the assistance of the International Society of Pharmaceutical Engineering (ISPE), and is an update on an earlier document. This document is organized in broad categories of unit operations (e.g., blending, drying, granulation etc.). For each unit operation, a table is provided in which equipment is classified by class (operating principle) and subclass (design characteristic). Generally, equipment within the same class and subclass are considered to have the same design and operating principle under SUPAC-IR and SUPAC-MR. A change from equipment in one class

[b] http://www.fda.gov/cder/guidance/cmc5.pdf

[c] http://www.fda.gov/cder/guidance/1721fnl.pdf

[d] http://www.fda.gov/cder/guidance/1214fnl.pdf

to equipment in a different class would usually be considered a change in design and operating principle. But equipment changes to a different subclass within the same class should be carefully considered and evaluated on a case-by-case basis. By these definitions, *encapsulating*, or the "division of material into a hard gelatin capsule" is an *operating principle*. That is, all encapsulators should have in common rectification, separation of caps from bodies, dosing of fill material/formulation, rejoining of caps and bodies and ejection of the filled capsules. However, the various methods of dosing the formulation represent different design characteristics and are considered *subclasses.* Thus, a change from a dosator machine to a dosing disc machine would constitute a change in subclass, but not of operating principle.

A survey of industry practices indicated that 64% of companies develop formulations using small-scale equipment of the same design and operating principle as the production equipment (12). In that same survey, about 18% of companies responded that they use small-scale development equipment of a subclass different from the intended production equipment. Company preferences appeared about evenly divided between dosator and dosing disc machines, with about 18% using both types of machines. The following sections address some of the issues involved in scaling-up or transferring within and between subclasses.

Scaling-Up Within the Same Subclass

In principle, scaling-up within the same subclass should be subject to minimal problems. In contrast to tableting where strain rate tends to be faster and dwell time and contact time tend to be shorter in higher output presses, higher output plug forming machines of the same manufacturer's series typically do not make plugs any faster than the lower output machines. That is because higher throughput is achieved in these machines primarily by increasing the number of dosing units. To illustrate that point, consider Table 1, which compares three sizes of Bosch GKF machines where pin movement or dwell time are reportedly similar across machines (Van Tol, 2005[e]).

The increased diameter of the powder bowl of larger machines and, therefore, of the turning radius of the dosing disc, may, however, influence the distribution of the powder over the dosing disc. For best weight variation, there may be an optimal flow criterion that should be met for dosing disc machines of this type, and that criterion may vary with turning radius. Kurihara and Ichikawa (54) reported a minimum point in the plot of the angle of repose versus coefficient of variation of filling-weight for a dosing disc machine (Höfliger Karg GKF 1000). This observation could perhaps be understood by recognizing that powder is distributed over the dosing disc by the centrifugal action of the indexing rotation (baffles are provided

[e] J. Van Tol, Robert Bosch packaging Technology, Minneapolis, MN, personal communication.

Table 1 Comparison of Three Bosch GKF Models

Model	Maximum rated output (capsules/hr)	Maximum cycle speed (cycles/min)	Powder bowl diameter (in.)	Number of tamping pins at each station
GKF 400	24,000	133	7.55	3
GKF 1500	90,000	125	13.4	12
GKF 2500	150,000	140	15.7	18

Source: From Van Tol, personal communication, 2005.

to help maintain a uniform powder level). Kurihara and Ichikawa (54) related the relationship between the angle of repose and weight variation to the degree of acceleration that takes place in disc movement, which, in turn, is dependent on dosing disc size and rotational speed. Their observations suggest that at higher angles of repose, the powders may not have sufficient mobility to distribute well over the dosing disc via the intermittent indexing motion; whereas, at lower angles of repose, the powder may be too fluid to maintain a uniform bed. However, this interpretation of their results may need qualification since they did not appear to make use of the tamping mechanism. Working with an instrumented GKF model 330, Shah et al. (21) observed that a uniform powder bed height was not maintained at the first tamping station owing to its nearness to the scrape-off device adjacent to ejection. However, more recent workers also have pointed to the need to properly calibrate the flow properties of formulations for this type of filling machine. Heda et al. (55) studied model formulations having different flow properties on a GKF 400 machine and proposed that Carr Compressibility Index values (CI%) should be in the range of 18–30 to maintain low weight variation. More poorly flowing powders (CI% > 30) were observed to dam up around the ejection station. Podczeck (56) noted that poor flowing powders display an ''avalanching behavior'' in front of the ejection station in which a powder mass alternatively builds up and then collapses in the manner of an avalanche at certain intervals of time. The net effect is that the powder over stations one and two can vary dramatically, thereby causing increased capsule fill weight variation (56).

The MG-2 series of dosator machines also exhibit similar plug forming parameters across machines with different production capacities. For example, the 16 station (up to 48,000 capsules per hour) and 64 station machines (actually a double 32 station machine; up to 200,000 capsules per hour) operate at the same RPM, have the same spacing between dosators, and have similar dosator penetration and withdrawal speeds, plug compression dwell times and plug ejection speeds (McKee, 2005[f]). Unlike the powder bed

[f] J. Mckee, Mg America, Fairfield, NJ, personal communication.

of dosing disc machines, the powder bed into which dosators dip to form plugs is scraped off neatly to a specific bed height. In the MG-2 continuous motion machines, the powder bed is an annular ring (''powder trough'') that rotates with the dosator turret (dosing head), but the two rotate at slightly different speeds. Because of this difference in rotational speeds, a plug is not formed from the same location in the powder bed until approximately 8–10 revolutions have occurred and the bed will have been restored and stabilized (McKee, personal communication, 2005). Maintaining a uniform powder bed density in dosator machines is essential for dosators to pick up uniform weights of powder. This difference in rotational speeds also causes the dosator to enter the powder bed at an angle, causing a furrow, rather than a vertical hole, to be formed. The axes of rotation of the annular powder bed and the dosing head are offset and the dosator turret has a smaller radius than the powder trough. Thus, as the turret rotates, dosators alternatively pass over the annular powder trough (to form plugs) and then over bushings bearing capsule bodies (to discharge plugs). See Figure 6.

The MG-2 Futura series of machines can be fitted with different numbers of dosators to give outputs ranging from 6000 to 96,000 capsules per hour. Because turret and annular powder bed dimensions would remain the same, few problems should be expected when scaling-up within this range on this machine. However, it is important to recognize that since the distance between dosators will increase when fewer than the full complement

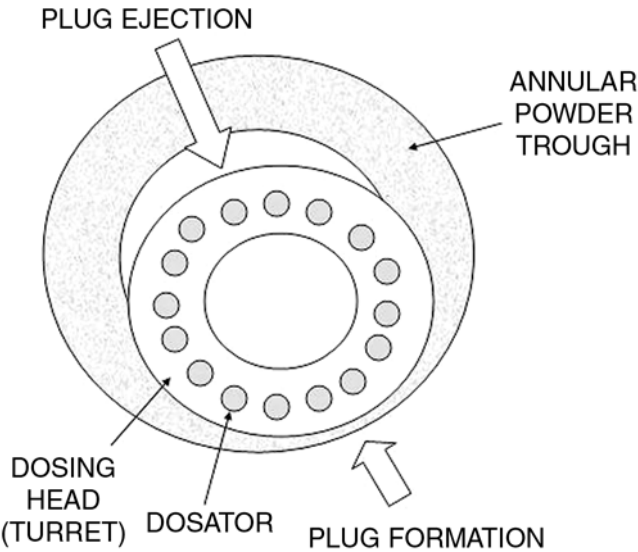

Figure 6 Diagrammatic representation of the plug forming and ejection stations of a MG-2 continuous motion filling machine.

of 16 dosators are installed, the number of revolutions needed to restore and stabilize the bed for each dosator will be longer than when the machine is fully tooled (McKee, personal communication, 2005).

Filling capsules on an MG-2 Futura fitted with four dosators, Desai et al. (57) found the dissolution of three drugs of varying solubility to be slower 45 minutes into the filling run compared to capsules sampled at the beginning of the run. The slowdown was greatest for the least soluble drug. The slowed dissolution was attributed to prolonged mixing by the propeller blade in the hopper, leading to increased coating of particles with hydrophobic magnesium stearate (57). A simulation study was conducted in which the capsule machine was left on for up to 60 minutes without filling capsules, during which time the formulation was being constantly mixed by the propeller blade in the hopper. In this study, capsules were hand-filled (to eliminate possible compression effects) at the the beginning and at the end of a run. Formulation changes can help resolve this problem. After a 60-minute run, dissolution from capsules filled from the hopper was significantly reduced from that of capsules filled before the start of the run. In a further experiment conducted with the intermediate solubility drug and using 15-minute mixing in a Hobart mixer to simulate over-mixing, no slowing of dissolution from hand-filled capsules was found when magnesium stearate (1% of formula) was replaced with an equal concentration of more hydrophilic lubricants (Stear-O-Wet or sodium stearyl fumarate). In a third study, the MG-2 machine was turned on to allow mixing in the hopper, and machine filling was activated for 10-minute periods of time at the beginning, after 30 minutes and after an additional 60 minutes of the run. The results of this study showed no slowing of dissolution when the magnesium stearate level was reduced to 0.25%, which appeared to provide sufficient lubrication. In another approach, replacing pregelatinized starch (10% in the formula) with equal concentrations of Explotab or Primojel resulted in no slowing of dissolution, even after over-mixing with 1% magnesium stearate in the formula (57).

During a trial production of 25 mg indomethacin capsules, Johanson et al. (58) reported both a segregation problem and an over-mixing problem on an MG-2 model G36/4 machine. The formulation was mixed using a planetary mixer. Magnesium stearate was added separately and mixed for five minutes. Drug content and dissolution were found to vary with time during the run. The authors concluded that the powder throughput was so slow at the mixing blade rotational velocity of 1 rev/min that over-mixing occurred. To solve both problems, the mixing blade was removed and the hopper was fitted with an insert to convert it to a mass flow hopper.

Harding et al. (33) proposed mixing in a Turbula high intensity mixer as a predictive stress test to determine the likelihood of encountering a dissolution problem on scale-up due to lubricant over-mixing. They found a

Table 2 Comparison of Compression Parameters

Machine type	Output (per hr)	Velocities (m/s)		
		Dosator (dipping)	Piston/tamp (compression)	Piston/tamp (ejection)
Zanasi AZ-20	15,000	0.242	0.12	0.453
	21,000	0.350	0.16	0.653
Macofar 13/2	6,600	0.301	0.22	0.272
	12,600	0.60	0.51	0.834

Source: From Ref. 3.

qualitative relationship between changes in the properties of a 500 g batch induced by mixing in a 2 L Turbula for six hours and the effect of a six-hour encapsulation run on a 10 kg batch of the same formulation in a Zanasi LZ-64 dosator machine.

Scaling-up within the same subclass but across different manufacturers of the equipment may also entail differences that could affect the success of the outcome. Consider the data in Table 2 for two different intermittent motion dosator machines. As can be seen, there are substantial differences in the compression and ejection velocities. Working with a Macofar simulator, Britten et al. (51) found that plug ejection speed had little effect on plug properties, but higher compression speeds led to reduced plug consolidation and lower weights. Possible differences in their powder handling and mixing mechanisms and powder throughput rates also could cause formulations to perform differently. Some machines may tend more to encourage segregation of certain formulations or may be more likely to over-mix magnesium stearate in the machine.

Transferring Between Dosator and Dosing Disc Machines

Scale-up from early development may involve not only larger-capacity filling machines of the same subclass, but also machines in different subclasses. Few studies have been reported comparing the formulation requirements of dosator and dosing disc machines. As discussed in the preceding sections, there are substantial differences in the way these two types of machines handle the powder feed and form plugs. Different rates of plug compression, different dwell times, and whether the plug is formed in one stroke (dosator machines) or multiple strokes (dosing disc machines) at least theoretically could cause differences in plug bonding and densification and dissolution. The goal of this section is to provide guidance to formulators who may wish to design formulations that can be run on either type of machine or who may need to consider transferring from one machine type to the other.

A Dosing Disc Machine May Be Able to Accommodate a Broader Range in Powder Properties

Bulk Density and Densification: The multiple tamp principle of the dosing disc machine appears more efficient at densification than the single stroke dosator machine (without vacuum densification). In a study comparing the same model formulations on an instrumented Zanasi LZ-64 and an instrumented Höfliger-Karg GKF-400, Heda et al. (55) found that similar fill weights could be attained on both machines, but the dosator machine required a piston height setting of 18 mm, as compared to the dosing disc height of 15 mm for the dosing disc machine.

Compactibility: Ridgway and Callow (59) long ago recognized that dosator machines would require a higher degree of compactibility due to the exposure of the plug from the open end of the dosator. Heda et al. (55) recently showed that certain model formulations produced higher weight variation when run on a Zanasi machine than when run on an H&K GKF machine and related that difference to a need for greater compactibility when running on the dosator machine.

Flowability: In their analysis of the running of model formulations on a Zanasi LZ-64 and H&K GKF 400 machine, Heda et al. (55) observed that an optimal degree of fluidity may be required for successful encapsulation on either machine. A CV% value of 20–30 appeared to be a suitable value for both machines, based on an analysis of weight variation. Highly free flowing powders that tend to flood can cause filling problems in both types of machines. In addition, such powders often do not form plugs well enough to be transferred by a dosator. Podczeck and Newton (60) concluded that such powders could be handled in a dosing disc machine by increasing the powder bed height.

Dosing Disc Machines May Have a Lower Lubricant Requirement: When transferring a formulation originally developed on a Zanasi machine to an H&K GKF-1500, Ullah et al. (61) found that the drug dissolved from the capsules filled on the dosing disc machine more slowly than when they were filled on the dosator machine. They proposed that shearing of the laminar magnesium stearate during the tamping step caused excessive coating of the formulation with the hydrophobic lubricant and found that the problem could be solved by reducing the initial level of lubricant from 1% to 0.3%. This decision was based on a study using a laboratory scale mixer/grinder to simulate the shearing action of the filling machine. Satisfactory dissolution was obtained with 570 kg and 1100 kg (full production) size batches using this reduced level of lubricant.

Comparing model formulations at equivalent magnesium stearate levels and compression forces, Heda et al. (55) observed that plug ejection

forces were lower on the H&K GKF 400 machine than on the Zanasi LZ-64. Based on ejectability, the dosing disc machine appeared to require about half as much magnesium stearate for the materials and conditions studied. This observation possibly reflects a greater shearing of magnesium stearate in the dosing disc machine, as proposed by Ullah et al. (61).

Formulations May Exhibit Different Dissolution Profiles: As discussed above, the same formulation run on the two types of machines may exhibit different dissolution profiles due to differences in the shearing of magnesium stearate, but, conceivably, other factors could also affect dissolution. Dissolution may be affected by differences in plug density/porosity that result from differences in such variables as compression force, dwell time, and rates of compression. In a dosator machine simulator, higher piston compression speed produced a less consolidated plug (51), and plug porosity was inversely related to piston compression force (18). In dosing disc machines, the added time under pressure that already-formed plug segments can experience at additional tamping stations may lead to further densification of ductile formulations (23).

Multiple tamping, as compared to the single compression step of a dosator machine, also may affect dissolution. Using an instrumented dosing disc machine (H&K GKF 330), Shah et al. (62) found slower dissolution of hydrochlorothiazide after two and again after three tamps at a particular tamping force compared to a single tamp at the same compression force. The effect was more marked at a compression force of 200 N than at 100 N. At 100 N, the mean pore diameter determined by Hg intrusion decreased from 12.8 μm after one tamp to 10.8 μm after two tamps. No further decrease in mean pore size was noted after a third tamp at 100 N. Interestingly, the inclusion of 4% of the super disintegrant, croscarmellose, effectively eliminated the effects of multiple tamps or compression force on dissolution.

In their study of model formulations filled using both an instrumented dosator (Zanasi LZ-64) and an instrumented dosing disc machine (H&K GKF 400), Heda et al. (55) compared the dissolution profiles from capsules filled on both machines. Two compression forces were compared: 100 N and 200 N. For ascorbic acid, they found two cases where the f_2 value was less than 50, suggesting that the dissolution profiles for those formulations are different when filled on the two machines with the same compression force. When dissolution profiles of hydrochlorothiazide from capsules filled on both machines were compared, the f_2 value was less than 50 for one formula at 100 N compression force. These differences in dissolution between the two machines indicated by the f_2 metric would suggest the need for a preapproval supplement, were this the outcome of a post-approval change in filling machines, since these machines belong to the same class, but different subclasses (53). The guidance also notes that such changes should be carefully considered and evaluated on a case-by-case basis, and places the

burden on the applicant to provide the scientific data and rationale at the time of change to determine whether or not a preapproval supplement is justified. The FDA reviews such data at its discretion.

GRANULATIONS

In a survey of industry practices, Heda (12) found that, as a matter of policy, 46% of the firms sampled favor direct filling of powders as a first choice over granulation prior to filling capsules. Thirty-six percent of firms allow formulators to make that decision at their own discretion, whereas 18% of firms favor granulation of all formulations prior to encapsulation. Yet, for half of the firms responding, only 0–10% of their hard shell capsule products are direct-fill powder formulations, and only 27% of firms reported that more than 50% of their capsules were developed as direct-fill formulations. Although some of these non-direct-fill formulations may be controlled release formulations, e.g., barrier-coated bead products, difficult powder formulation problems may, at least in part, account for this observation.

The standard wet and dry methods used to granulate powders prior to tableting are used. When formulators granulate prior to encapsulation, they frequently do so to increase density. Thus, the weight that can be filled in a given size capsule can be increased, or a smaller capsule size can be selected. However, granulation can enhance a number of other processing characteristics and properties. Flow and compression properties of formulations can be improved. Dustiness and particle adhesion to metal surfaces can be reduced. Granulation also increases robustness by reducing variability in the physical properties of raw materials. Wet granulation may improve wettability and drug dissolution through hydrophilization (63,64). Common binders used in wet granulation, such as pregelatinized starch and polyvinyl pyrrolidone, are hydrophilic and can be expected to deposit on particle surfaces where they may enhance wettability. Granulation can improve content uniformity by holding drug particles in granules, so that the formulation can be handled without loss of blend quality. Moreover, the binder liquid phase in wet granulation provides a convenient vehicle by which to introduce and uniformly disperse a very low dose drug throughout the mass. Among the firms sampled by Heda (12), 64% favored wet granulation for capsule formulations, 18% favored dry granulation and the remainder had "no policy."

In general, the same principles as apply to filling powders should apply to the filling of granulations, but with some qualifications. For instance, Podczeck et al. (60) found that an acceptable filling performance was always achieved when different granule size fractions of Sorbitol instant® were filled on both a dosing disc (Bosch GKF 400) machine and a dosator (Zanasi AZ 5) machine. However, the dosing disc machine, which depends less on forming firm plugs, seemed slightly better suited to the coarser granule size fractions than the dosator machine. On the other hand, the dosator machine

invariably produced plugs that were denser than the formulation maximum bulk density, suggesting that this dosing principle might be more useful for granulations where the dose is large or where smaller capsule size is desired.

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14

Scale-Up of Film Coating

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INTRODUCTION

Overview of Coating Processes

A comprehensive overview of pharmaceutical coating (materials, formulations, and processes) has been given by Porter and Bruno (1). It should be noted that there has been a steady transition in the pharmaceutical industry, beginning with sugar coating, moving to film coating, and finally arriving at aqueous film coating. Sugar coating can be characterized as a relatively complex but noncritical process. Complexity stems from the multiplicity of coating formulations used during one process and the sequencing (dosing, distributing, and drying) that must take place for each application of coating liquid; noncriticality is associated with the fact that precise control over process parameters (air volumes, temperatures, spray rates, etc.) is not a prerequisite for success in the process. In contrast, film coating is a relatively simple but critical process. In this case, simplicity relates to the need to use fewer (and sometimes only one) coating formulations during the process, which are usually applied in a continuous but controlled manner; criticality is manifest by the need to identify and control a range of key processing factors, especially when applying water-based coating formulations.

Although both sugar and film coating are utilized by a significant number of pharmaceutical companies worldwide, the film-coating process is the one most often preferred today.

Film coating was formally introduced into the pharmaceutical industry in the middle of the last century. Initially intended to provide a means for more rapidly applying coatings to pharmaceutical tablets, it has readily been adapted for coating other types of products (such as pellets, granules, powders, and capsules). In general terms, film coating is a process whereby a polymer-based coating is applied to the substrate, such that:

- the rate of application of the coating fluid and the drying rate are carefully controlled
- the coating material is uniformly applied to the surface of the substrate
- the quality and functionality of the applied coating are both maximized and reproducible

Although film coatings are most often applied for their aesthetic qualities, they have an important role to play in improving product stability and robustness, as well as enhancing flavor attributes, facilitating ingestion, and modifying drug-release characteristics.

Film-coating formulations encompass those that are expected to allow a drug to be rapidly released from the dosage form, those that may possess special barrier properties (with respect to, e.g., moisture or oxygen), and those designed to modify drug release characteristics and facilitate drug targeting. As such, these coating formulations are exemplified by:

- organic-solvent-based solutions of polymers (1)
- aqueous solutions or dispersions of polymers (2)
- hot-melt systems (3)
- powder coatings (3)

Despite the apparent variety expressed by these options, aqueous systems hold a dominant position in the pharmaceutical industry at this time. As a consequence, serious constraints are often imposed on the products being coated, the coating formulations used, and the coating processes that are adopted, with the result that scaling up the coating process can present serious challenges.

It is one of the intriguing contradictions of film coating, especially when considering aqueous processes, that, in order to create a more robust product, the initial product has to be designed to survive a process that becomes progressively more stressful the larger the scale of process employed. Such stress is associated with both the environmental conditions within the process and the attritional effects to which the product being coated is subjected. It is often the failure to appreciate these issues that reduces the likelihood of achieving complete success during the scale-up process. It is also worth remembering that process scale-up is not a one-time event; rather, it can be an ongoing process that is driven by the need to

increase capacity and cut operating costs throughout the product life cycle. Under these circumstances, the need to modify a less-than-optimal process to accommodate ongoing scale-up issues may face regulatory constraints that prevent total success being achieved. There is no substitute, therefore, for taking great steps to confirm the robustness of both formulations (core and coating) and coating processes, especially since critical decisions may have been made on the basis of laboratory-scale trials conducted early on in the development process. This subject will be further discussed later on this chapter.

Film Coating—Equipment Concepts

At the heart of any coating process is the coating vessel, which can take one of two forms:

- coating pans
- fluid-bed coating equipment

In the beginning, film-coating equipment was commonly derived from that used in the sugar-coating process, namely, conventional coating pans. The early days of film coating, however, coincided with the introduction of a fluid-bed coating process developed by Dale Wurster (4), and this quickly became adopted for many film-coating operations. The growing demand, however, to find alternatives to the use of organic solvents, together with the introduction of the side-vented coating pan (initially in the form of the Accela-Cota), has resulted in coating pans being preferred for coating tablets, while fluid-bed processes are more commonly employed for coating multiparticulates (5). While a veritable plethora of coating equipment is available in the industry today (especially since generic versions of many of the pioneering developments are now available), the basic concepts of panning equipment are shown in Figure 1, and those of fluid-bed equipment in Figure 2.

The availability of such a variety of equipment often adds an extra degree of complexity to the scale-up process. Geographical preferences in equipment selection (often as the result of a desire to source locally and take advantage of vendor support programs) can mean that the manufacturing-scale equipment available may differ from the equipment used during process development, even when the equipment design is essentially based on the "same operating principles."

Thermodynamics of the Film-Coating Process

Since the majority of film-coating operations around the world utilize aqueous coating processes, it is often useful to apply thermodynamic models to the process. In this way, the development-scale process can be fundamentally characterized, based on application of the first law of thermodynamics, as suggested by Ebey (6), allowing more accurate predictions for operating

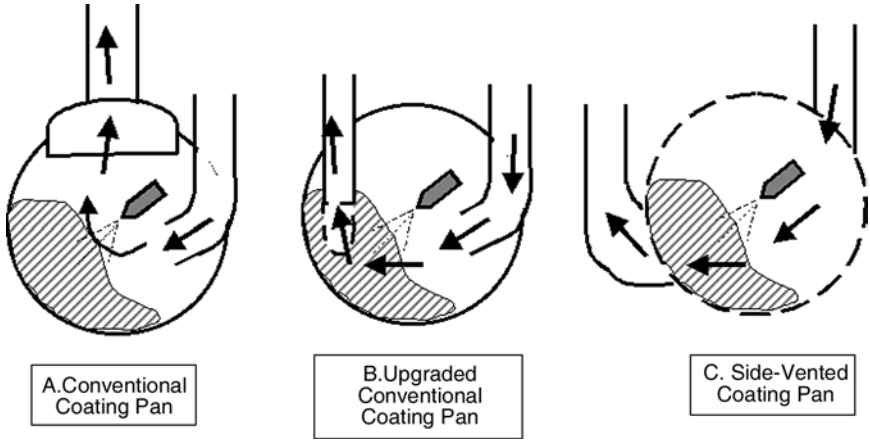

Figure 1 Schematic diagram highlighting the basic concepts of pan-coating equipment.

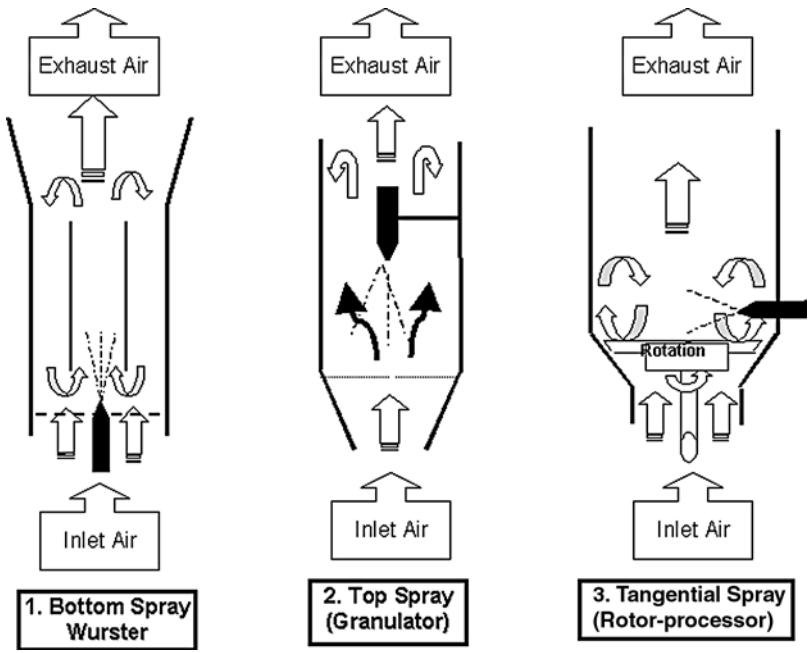

Figure 2 Schematic diagram highlighting the basic concepts of fluid-bed coating equipment.

the production-scale process in a manner so that the two processes are essentially equivalent.

Ideally, of course, it would be desirable to operate all processes under constant conditions. Such an ideal is often beyond the practical capabilities of many film-coating operations. Application of the concepts proposed by Ebey, however, usually permit predictive processing adjustments to be made in order to allow for natural variation in the coating process. For example, for a process where the moisture content of the processing air varies from day to day, season to season, etc., it is possible to determine what changes, for example, in spray rates, inlet-air temperatures, or inlet-air volumes are required to maintain the product temperature at the predetermined set point. By way of example, the initial process conditions outlined in Table 1 represent process conditions for an aqueous film-coating process conducted in a laboratory-scale coating pan where the moisture content of the inlet air is such that its dew point is 4.5°C. The modified conditions in the same table exemplify how the process can be adjusted by changing the spray rate to maintain an equivalent process when the moisture content of the inlet air has increased (to where the dew point is now 15.5°C).

While mathematical tools such as those described by Ebey are useful for predicting adjustments in order to maintain the equivalency of two processes, it must be remembered that these tools are evaluating the macroenvironment within those processes. The changes that may, however, be taking place at the microscopic level (as, e.g., that which exists at the precise moment when droplets of coating liquid make contact and begin to interact with the surface of tablets, pellets, etc.) are much more complex and much less predictable. Mathematical models as suggested here, however, still have value in making predictions that can often reduce the actual number of coating trials that need to be performed, even though

Table 1 Example of Application of Thermodynamic Model to Predict Adjustments in Process Conditions When the Inlet-Air Moisture Content is Increased

Process parameter	Initial process	Modified process
Spray rate (g/min)	75	72
Coating solution solids content (% w/w)	15.0	15.0
Inlet-air temperature (°C)	70	70
Inlet-air dew point (°C)	4.5	15.5
Process-air volume:		
(cfm)	200	200
(m^3/h)	350	350
Exhaust-air temperature (°C)	43	44
Environmental equivalency factor (EE)	1.761	1.761

they cannot be used to predict empirical results, such as coated tablet aesthetics.

Boundaries of the Film-Coating Process

Unlike the processes described elsewhere in this book, the film-coating process is inherently much more complex, since the list of parameters that contribute to overall success is, potentially, exhaustive. Thus, the complexities of the scale-up process are potentially more challenging. In basic terms, these three components of the film-coating process all contribute, in a very much interactive manner, to the overall success of the process:

- the core (ingredients, size, shape, surface chemistry, and physical attributes, etc.),
- the coating (ingredients, solvents, surface chemistry, rheology, and tackiness, etc.), and
- the coating process (equipment design, process parameters employed, maintenance, and calibration programs, etc.).

The inherent complexities of this process are well illustrated by the process operational boundaries highlighted in Figure 3. Although this diagram specifically references tablet coating in a side-vented pan, the concepts

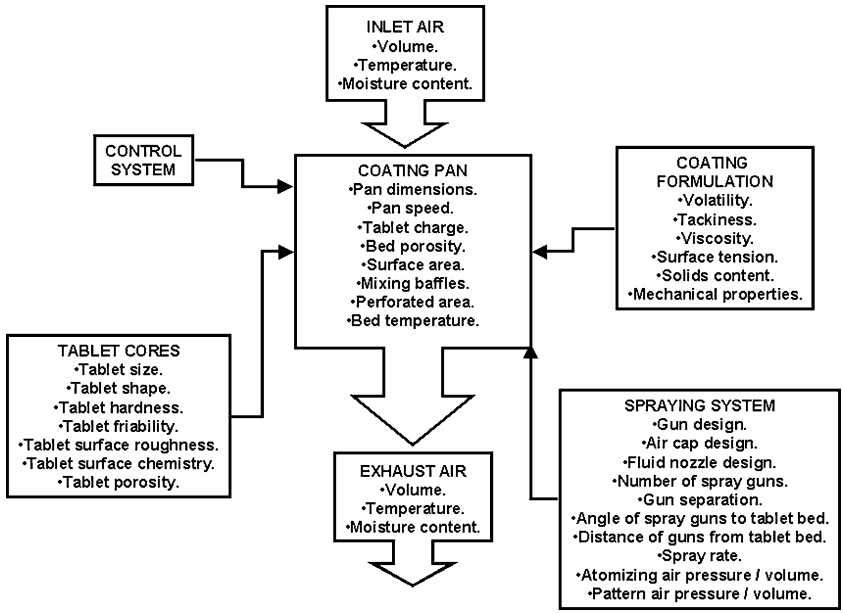

Figure 3 Outline of the operational boundaries of a film-coating process.

are applicable to the film coating of all types of products in a wide variety of coating machines.

SCALING-UP THE COATING PROCESS

General Factors to Consider

The introductory section has provided the reader with some idea of the complexities of pharmaceutical coating processes, especially those relating to the now predominant aqueous film-coating process. These complexities can be transformed into serious challenges that face the scientists and engineers charged with the responsibility for scaling up the coating process. Unlike that associated with many other unit operations, scale-up of the coating process involves much more than just dealing with larger batch sizes and faster throughputs. The application of coatings, often being the penultimate step to packaging, can leave a long-lasting impression in terms of product appearance and product performance (both in terms of functionality and stability). Additionally, once the coating stage is reached, there has already been a large investment (of time and money) in that batch of product.

In a somewhat simplistic way, the scale-up of a coating process typically involves:

- taking a laboratory-scale process (hopefully, one that has been appropriately optimized) and transferring the processing technology first to the pilot scale, and ultimately to full production scale
- further optimizing the process on the larger scale to take into account issues whose influence could not easily be predicted during earlier process-development activities

Irrespective of the type of coating process used, the potential process changes that commonly occur on scale-up include:

- increased batch sizes
- increased attritional effects
- increased spray rates
- increased number of spray guns (or change from a single- to a multiple-head nozzle)
- increased drying air volumes
- increased processing times (per batch)

Many of these parameters are quite predictable, especially when applying some of the thermodynamic concepts described earlier. The increased processing time, which brings with it increased exposure to stressful conditions (both mechanical and as a result of environmental conditions used in the process, especially when that process is aqueous-based) is much more

unpredictable, and is often the root cause of much angst during the preparation of early commercial batches.

The Robustness Factor

In spite of the issues outlined in the previous section, all too often the amount of time spent on formulation and process design is inconsistent with the impact that is felt when performance in the coating operation fails to meet expectations. More attention in this regard is usually paid when the applied coating has some specialized functionality (such as improving product shelf life, or modifying drug release characteristics); however, even when the purpose of the coating is primarily for aesthetics and product identification (in which cases, poor coated-product quality is unlikely to impact product efficacy), failure to meet certain visual standards all too often results in batch rejection, leading to:

- discarding the batch (often determined on the basis of balancing recovery costs with the inherent value of the batch)
- reprocessing the batch
- sorting the batch to remove defective material

In each of these cases, there is a certain financial cost associated with potential product loss, reprocessing, and work in process.

Clearly, therefore, there is a strong incentive to ensure that:

- the formulations (core and coating) are sufficiently robust to meet the needs of the operation. This requirement is all the more important when viewed in terms of the increased (but often ill-defined) stresses to which the product is subjected on scale-up
- critical elements of the coating process, and their impact on final product quality (in the broadest sense), have been determined and taken into account during process optimizationa

While these requirements seem obvious, they are often ignored. Critical decisions with respect to design of coating formulations and processes are frequently made on the basis of data produced from small-scale processing trials. The consequences of such decisions only become apparent after product approval, thus resulting in the fact that the changes required to rectify matters are often very much constrained by regulatory issues (although these may be diminished to a degree as a result of the issue of the SUPAC Guidances).

One of the elements of film coating that attracts much attention at technical symposia is that dealing with "troubleshooting." This very fact is a clear indication of how poorly the matters described here are considered. While it is certainly important to understand the issues that can potentially lead to problems, and explore recovery options, the very idea that troubleshooting needs to be considered is clearly an admission of failure during

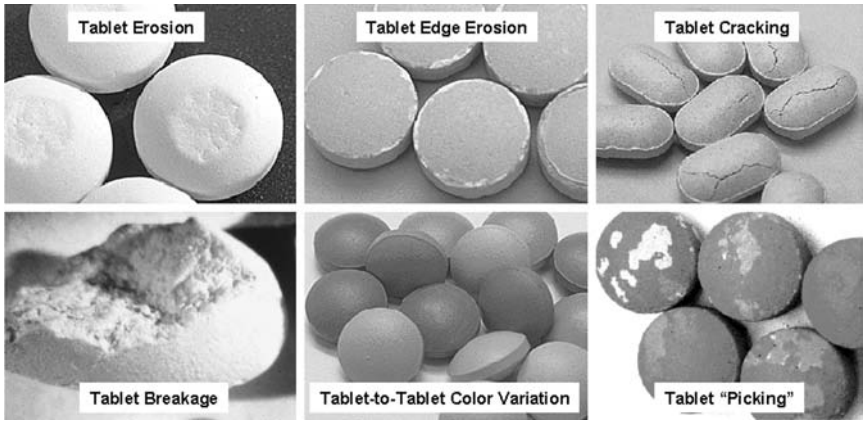

Figure 4 Common examples of film-coating problems that trigger troubleshooting exercises.

critical stages of product and process development. The photographs shown in Figure 4 provide typical examples of problems which crop up all too often under the troubleshooting banner, and usually relate to some aspect of the coating process employed.

Opportunities for Process Optimization and Use of Expert Systems

Much of the data developed during product and process development is often empirically derived and, as such, reflects the relative experience and preferences of those responsible for that development process. While application of such experience can be of tremendous value, it is not unusual to find that each new product that is being developed, or process refinement being employed, has inherent idiosyncrasies that reduce the relevance of prior experience. In order to create a ''robust'' product and process, personal bias has to be removed, and, instead, decisions must be made based on scientific validity. All too often, the phrase ''we have fully optimized the product and process'' is used to describe a situation where decisions have been made on the basis of an iterative process where process (and formulation) variables have been studied in a ''trial and error'' manner, changing one parameter at a time. This process, often called one of ''successive approximation,'' is followed until an acceptable process has been achieved. The problems associated with employing such techniques include:

- a truly optimal process (or product) is rarely achieved,
- a comprehensive database that relates to the critical features of that process is rarely obtained, and

- subsequent decisions that demand further process modifications (e.g., on the basis of meeting operational requirements to improve process productivity or reduce process costs) often confound the "optimization" process.

The answer to these concerns involves the employment, during the development process, of techniques that utilize a Design of Experiments (DOE) approach. The application of such techniques has been well documented in the published literature. For example, Porter et al. (7), in examining a side-vented pan process, were able to produce unambiguous quantitative results that defined how, inter alia, uniformity of distribution of the coating and coating process efficiency could be maximized while meeting other objectives with respect to coated product quality (e.g., gloss, smoothness, and residual moisture content). Turkoglu and Sakr (8), in studying the application of a modified-release coating to pellets in a rotary fluidized-bed process, determined that coating temperature and atomizing air pressure were key factors that influenced drug release from the pellets when applying an aqueous ethylcellulose dispersion. Finally, Rodriguez et al. (9) employed similar techniques when studying the thermodynamics of an aqueous film-coating process performed in a GS Coating Systems pan.

Ultimately, the real advantage of utilizing a DOE approach during process development and optimization is that:

- all critical process parameters can be identified in a way that removes personal bias
- a truly optimized process can be developed which has a sufficiently sound scientific basis to satisfy queries from regulatory agencies
- further process refinements, particularly during scale-up, can be made in a much more predictable manner when faced with the need to meet specific operational constraints

Clearly then, adopting a formal, scientifically valid approach to designing and optimizing a particular coating process provides a good foundation ultimately for scaling up that process. That having been said, in these days of globalization, the scale-up process can involve technology transfer from one department to another that may be geographically remote from it. In such a situation, the department on the receiving end of the transfer process may be in a technical void with respect to critical knowledge about that process. Under these circumstances, ready access to such technical information (on a 24-hour basis) is often of paramount importance if success in the scale-up process is to be achieved and maintained. Considering that such knowledge may reside with only a few key people, the challenge is how to provide the necessary access. Conventional wisdom is to prepare exhaustive technical reports, either in hard copy or electronic form, than can be distributed as needed. In the present environment, however,

instant access to information, utilizing a user-friendly approach, is often demanded. One such approach that is gaining more attention in the pharmaceutical industry involves the application of expert systems. Fundamentally, these systems consist essentially of a computer program that makes decisions or recommendations based on knowledge gained from experts in the field. Such programs are usually customized to fit a given situation, and can utilize tools such as artificial neural networks, rule-based systems, decision trees, etc. The application of Expert Systems to pharmaceutical processes (including film coating) has been described by Rowe (10), and the commercial availability of such systems has been demonstrated (11).

So far, the discussion has centered on providing a description of the basis for typical film-coating processes, outlining some of the critical issues that need to be considered when contemplating process scale-up, and identifying some useful tools that may be employed to facilitate that process. Clearly, there is no substitute for careful preparation, and the benefits of doing so can best be illustrated by reference to case studies that exemplify scale-up studies that have been successfully concluded. In this regard, the case studies that will be discussed involve scaling up a process involving:

- coating of tablets in a pan process
- coating pellets in a fluid-bed process

Scaling-Up a Pan-Coating Process

Introduction

It should be quite clear now that time and money spent designing a robust process (where all of the critical process factors have been defined and their impact well documented) has the potential to save time and money later on, especially during the time leading up to, and immediately after, product launch. Designing an optimal process also has great benefit in the training of process operators so that they become well informed about the critical constraints of that process.

If a particular process is going to be used for a range of products that have similar characteristics, then time spent optimizing that process provides benefit many times over. There will, however, be times when a particular product has special needs that will mean that a well-optimized process may have to be further refined to meet those needs. Such a requirement is particularly evident when a coating process that has been designed for the application of conventional coatings (where aesthetics may be high on the list of attributes defining product quality) is now required to be adapted for the application of highly functional coatings, such as modified-release coatings (in which case, drug release characteristics will assume a much greater degree of importance).

Table 2 Coated Product Attributes and Coating Process Characteristics That May Be Used as Objectives to Develop an Optimal Process

Coated tablet attributes		Coating process characteristics
Aesthetic	Functional	
High gloss	Drug release characteristics meet target requirements	High (and reproducible) process coating efficiency
Smooth coating	Coated product meets stability requirements	High uniformity of distribution (on a weight basis) of coating from tablet-to-tablet
Good color uniformity	Effective taste masking is achieved (if required)	High productivity
Absence of edge chipping	Coated tablet meets target strength requirements	
Absence of film cracking		
Absence of logo bridging		
Absence of twinning		
Absence of picking		

Some key attributes of coated products and coating processes that may well be used to set objectives for optimizing a coating process are shown in Table 2. In many cases, the attributes as listed are very subjective, and thus must be defined in clearly measurable terms if they are to be used as the basis for process optimization. Additionally, meeting defined objectives may equally be dependent on the existence of certain coating and tablet formulation attributes. Nonetheless, while the information listed in Table 2 is not meant to be all-inclusive, it does provide an idea of the types of responses that could be used as a basis for optimizing a coating process.

When optimizing a coating process, however, a major challenge that must be faced involves selecting the appropriate process variables that must be examined. Reference to the operating boundaries of a typical coating process shown in Figure 3 clearly indicates that the list of potential variables to be studied is quite extensive. In order to create a manageable design of experiments program, the list of variables to be studied should not typically exceed four or five, otherwise the number of coating trials to be undertaken becomes prohibitive. Thus, attention should be focused only on those variables that have a critical role to play. Reducing the number of variables to a manageable level can be accomplished in a number of ways, including:

- fixing as constants those variables that are not open to change (e.g., selecting a particular type of coating pan, spray gun, mixing baffle design, pan loading, etc.)

Table 3 Process Parameters Examined in a Study Designed to Optimize a Coating Process Based on the Use of a 24″ Laboratory Side-Vented Coating Pan

Coating process variable	Variable range setting
A. Fixed operating parameters	
1. Pan loading (kg)	15.0
2. Drying air (cfm)	Inlet: 250; exhaust: 300
3. Coating system	Opadry II
4. Quantity of coating applied (% w/w)	3.0 (theoretical)
5. Pattern air pressure	
(psi)	30.0
(bar)	2.1
B. Variable operating parameters	
1. Solids content of coating suspension (% w/w)	10–20
2. Inlet-air temperature (°C)	60–90
3. Spray rate (g/min)	35–75
4. Atomizing air pressure	
(psi)	22–60
(bar)	1.5–4.1
5. Pan speed (rpm)	8–20
6. Number of spray guns used	1 or 2

- applying a preliminary screening technique, where a larger number of variables can be studied in a much more superficial manner. This approach enables the critical variables to be identified and then used as the basis for a more comprehensive evaluation

Earlier reference was made to published articles that described the use of optimization techniques for coating processes. In particular, the one presented by Porter et al. (7) provides a useful example of how aesthetic, functional, and processing issues can be dealt with. The key elements of the study that formed the basis for this article are listed in Table 3, while typical results obtained in this study are summarized in Table 4. From these data, it is possible to optimize the coating process with respect to:

- aesthetic qualities (gloss and coating smoothness) of the final coated tablet
- potential impact on final tablet stability (as this relates to product temperatures experienced in the process and residual coated tablet moisture content)
- process efficiencies (with respect to actual vs. theoretical amount of coating applied, and uniformity of distribution of the coating)

Table 4 Typical Results Obtained in Optimization Study

Response measured	Response units	Response ranges
Uniformity of distribution of coating material	% RSD	11.88–59.59
Coating process efficiency	%	26.23–99.37
Roughness value of applied coating[a]	R_z, (μm)	7.76–15.90
Gloss value of applied coating[b]	G_u at 60° angle	2.60–3.78
Final moisture content of coated tablet[c]	% w/w	0.10–5.33
Exhaust temperature of coating process	°C	32.8–57.3

[a]The higher the value, the rougher the coating.
[b]The higher the value, the glossier the tablets.
[c]Initial uncoated tablet moisture content was 3.0% w/w.

An important fact to be recognized, however, is that an extensive database relating to the coating process in question has been established, and key process variables (including their interactive effects) have been identified, providing a sound platform from which to begin the scale-up process.

Predicting Scale-Up Issues

Once an appropriate laboratory-scale process has been established, many of the key elements of the process should have been determined. Some operating parameters (such as inlet-air temperature, coating formulation to be used, and solids content of the coating solution/suspension) can be directly translated to the larger-scale process. Others, however, will have to change, and these include:

- drying-air volume
- pan speed
- pan loading
- number of spray guns to be used
- gun to tablet-bed distance
- spray rate
- spray gun dynamics

Drying-air volume: Drying-air volume, although potentially variable, is often selected based either on the recommendations of the vendor of the equipment to be used or on the basis of the optimum conditions designed for the air-handling system that has been installed. The supply and exhaust air fan speeds should be set, based on the equipment used, to meet the negative pressure pan settings that are usually recommended. Once the appropriate drying-air volume has been established, this setting becomes a driver for other key processing variables, such as spray rate (see later discussion).

Pan speed: Selecting appropriate pan speeds often becomes more of a challenge than is really necessary. Clearly tablet motion, a factor influenced greatly by pan speed, can be a major issue when it comes to potential tablet breakage, edge wear, and surface erosion. On the other hand, according to data established by Porter et al. (7), the uniformity of distribution of the applied coating is also greatly influenced by pan speed, with the higher pan speeds being better in this regard. Consequently, there is a great incentive to design tablet cores so that they can withstand high pan speeds in order to allow coating uniformity to be fully maximized.

Typically, those pan speeds that are selected on scale-up are often lower than are truly optimal in recognition of the fact that attritional effects do increase with increasing scale of process. Nonetheless, a good "rule-of-thumb" based on pan speeds used on the laboratory scale and dimensions of the laboratory-scale equipment is to calculate the linear velocity of the tablets in the coating pan, and then to determine the pan speed on the larger scale which will give an equivalent linear velocity. In this way, tablet dwell time in the spray zone on the larger scale will be equivalent to that achieved on the smaller scale, and full benefit can be taken of the optimization strategies used on the smaller scale to maximize uniformity of distribution of the coating. An example of how pan speed can be determined on scale-up is shown in Table 5.

Pan loading: In general, defining appropriate pan loading should not be a troublesome issue. A coating pan of given dimensions is designed to hold a certain charge of tablets. Unfortunately, pan loadings are usually defined in terms of *volume* fill, rather than by weight. Thus, the optimum pan loading by weight will vary from product to product, depending on the *apparent density* (which takes into account the mass/volume ratio of an individual tablet, as well as the shape and size of that tablet) of that product. Even allowing for such product variation, calculating optimal pan loadings should not be a serious challenge. The difficulty arises, however, for these reasons:

- On the laboratory scale, it is not too difficult to ensure that a pan is appropriately loaded. Even when only a very small amount of product is available, this problem can be dealt with by bulking up active tablets with placebos to make a full charge.
- On the production scale, pan loading often has nothing to do with the ideal loading for the pan, but rather with the total batch weight of the compressed tablets, and how evenly these can be divided into a whole number of pan loads. For example, if the total batch weight is 500 kg, and these tablets are to be coated in a pan that optimally holds 120 kg per run, then the instructions will call for *five* pan loads of 100 kg each to be coated. The result is that each coating run will have each pan underloaded by about 16%.

Table 5 Estimating Pan Speed on Scale-Up

Parameter	Pan size			
Pan diameter	24 in. (60 cm)	36 in. (90 cm)	48 in. (120 cm)	60 in. (150 cm)
Typical pan rotational speed ranges (rpm)	5–20	3–17	2–15	2–11
Pan circumference	75 in. (190 cm)	115 in. (290 cm)	150 in. (380 cm)	190 in. (480 cm)
Peripheral pan speed at 10 rpm	12.5 in./sec (31.8 cm/sec)	19.2 in./sec (48.8 cm/sec)	25.0 in./sec (63.5 cm/sec)	31.5 in./sec (80.0 cm/sec)
Projected pan rotational speed at a peripheral speed of 12.5 in./sec (31.8 cm/sec)[a]	10	6.5	5.0	4.0

[a]This example is based on the rotational speed of 10 rpm used in a laboratory-scale coating pan.

In the example shown, a 16% underloading may not seem to be too much of a problem, but potentially critical issues that may arise (especially if the degree to which the pan is underloaded is even greater than the amount shown in the example) include:

- The possibility that, in a side-vented coating pan, there may not be enough tablets in the pan to ensure that the exhaust air plenum is completely covered (in which case, drying air will take the path of least resistance and flow directly towards the air plenum, rather than passing through the tablet bed). With some designs of coating pan, this potential problem may be obviated by the placement of a sliding damper in the exhaust air plenum, so that the exposed part can be sealed off.
- The potential that the side walls of the coating pan, or even baffles, become more exposed to the spray, causing coating liquid to build up on exposed metal surfaces, often with the result that tablets will stick to these surfaces. Again, with some foresight, changing the gun-to-bed distances, gun spacing, or indeed, the number of guns

used can minimize this problem. These solutions are likely to be utilized if, for a particular product, the pan loadings are relatively constant. In situations where compression batch weights frequently vary, then such corrective measures are less likely to be employed.

- The likelihood that when the pan is significantly underloaded, as baffles move through the tablet bed as the pan rotates, the surface of the tablet bed will move sufficiently to change the gun-to-bed distance. This situation, as will be seen later, could potentially change the characteristics of the spray droplets that are impinging on the surfaces of the tablets.
- As baffles become more exposed, and as pan speeds are constantly adjusted to keep the tablets in motion (more of a challenge in an underloaded pan), there is increased risk that tablets will become damaged.

Thus, during product and process development, even though compression batch weights are often defined in terms of the capacities of blenders, granulators, dryers, etc., there is sufficient justification, when the product is to be coated, to keep in mind the capacities of the coating pans that will be used.

Number of spray guns to be used: In any film-coating process, it is critical to ensure that the spray zone is optimized with respect to these key criteria:

- making sure that the full width of the tablet bed is covered, so that few, if any, tablets on the surface pass through the spray zone without receiving some coating
- setting up each gun (in terms of atomizing and pattern air) so that maximum coverage is achieved without compromising the quality (in terms of droplet size, size distribution, droplet density, and relative "wetness") of the atomized coating liquid
- avoiding overspray on to the pan sidewalls

This being the case, a major decision that has to be faced is: How many spray guns should be used? The answer may well depend on the type of spray guns available. As will be seen in later discussion, some spray guns have greater capabilities than others in achieving broader coverage without compromising spray quality.

Sight should not be lost of the possibility that, on scale-up, the type of spray guns available on the production-sized equipment may be different that those used on the lab scale. This situation may arise because:

- the spray guns used on the laboratory scale are not capable of achieving the spray rates required, or maintaining effective atomization at those higher spray rates, on the larger scale

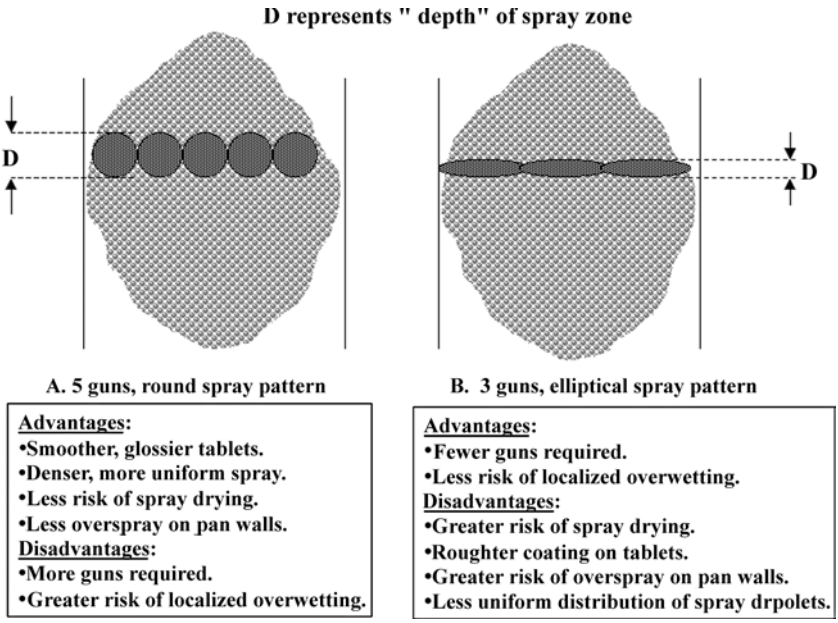

Figure 5 Influence of typical spray patterns on the number of spray guns used.

- scale-up may involve transfer to a manufacturing site that is geographically remote from that where process development was undertaken, and preference may have been shown for locally sourced spray guns

Unfortunately, scant attention is often paid to the need to minimize the number of changes that take place on scale-up, and this may especially be true in the case of spray-gun selection where, all too often, one type of spray gun is assumed to be very much equivalent to another. Again, as will be seen later, such equivalency may be far from true.

Concluding, therefore, that the main objective is to maximize bed coverage, issues that greatly influence the choice in number of spray guns used will be those as shown in Figure 5, where broader coverage per gun may well reduce the number of guns required, while more restricted coverage, often chosen in attempts to produce better coated tablet quality (in terms of coating gloss and smoothness), will necessitate the use of a larger number of guns. The data listed in Table 6 illustrate how spray pattern can influence coated tablet quality, with round spray patterns tending to produce smoother coated tablets, although with the increased risk that localized overwetting can occur, resulting in greater likelihood of sticking and picking. Clearly, the main objective is to avoid problems like those

Table 6 Influence of Spray Pattern Used on Tablet Quality

Polymer concentration (% w/w)	Atomizing air pressure	Spray pattern shape	Mean coating roughness, R_a (μm)	% Tablets showing defects (picking or sticking)
9	40 psi	Elliptical	2.72	24.0
	(2.8 bar)	Round	1.68	26.0
9	60 psi	Elliptical	2.53	4.5
	(4.1 bar)	Round	1.44	35.0
9	80 psi	Elliptical	2.29	2.5
	(5.5 bar)	Round	1.29	35.0
12	60 psi	Elliptical	3.51	2.0
	(4.1 bar)	Round	2.07	9.0

shown in Figure 6, where ineffective bed coverage leads to increased opportunities for tablets to pass through the spray zone without receiving any coating.

Gun-to-tablet-bed distance: There are very few examples of a truly scientific approach being taken to establish appropriate positioning of spray guns inside coating pans (unlike with fluid-bed coating machines where gun

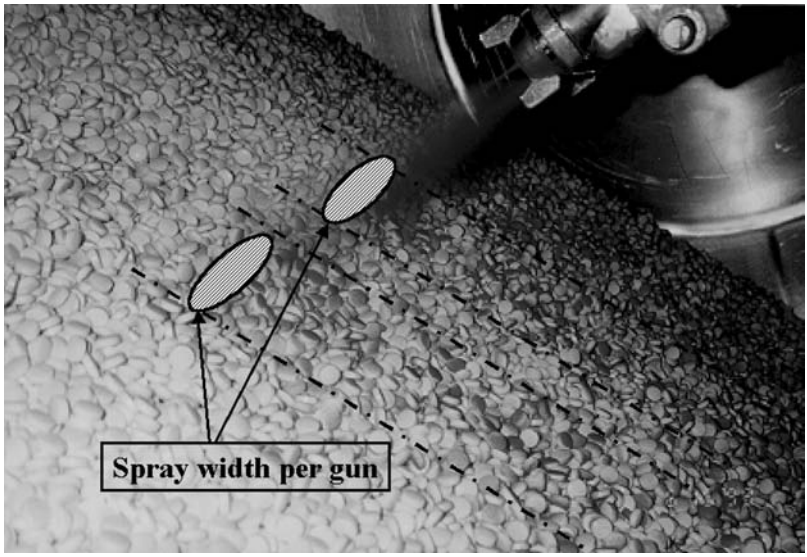

Figure 6 Example of how using too few spray guns leads to poor bed coverage.

location is more often predetermined). Typically, with the help of rudimentary positioning tools, such as a ruler, the operator is left to set up gun position by eye. Gun positioning needs to be optimized to:

- ensure that optimal, and reproducible, bed coverage is achieved
- facilitate broad coverage while providing maximum surface drying time (before tablets on the surface of the bed "fold under" and get mixed into the tablet mass)
- achieve reproducible (from run-to-run) spray droplet characteristics as they arrive at the tablet surface (see later discussion)

It is therefore quite surprising that this feature of equipment set-up often receives scant attention.

It is also interesting to note that spray gun-to-tablet-bed distances are often different in production-scale equipment than they are in that used in the laboratory. Fundamentally, if this parameter has been optimized appropriately during process development, then there is no reason not to believe that these distances should be the same irrespective of the scale of the process used. Nonetheless, the rationale for the existence of differences includes:

- On the laboratory scale, because of geometric constraints, there is often very little opportunity to optimize the gun-to-bed distance, and thus this parameter takes on a fixed setting often defined by personal preference. Once a move is made to the production scale, there is more opportunity to reconsider gun positioning (although logic does not always prevail).
- On the production scale, only a suboptimal number of guns may be available, with the result that the guns are moved further back to ensure that appropriate bed coverage is achieved. This requirement may also be dictated by use of different types of spray guns on the larger scale that also necessitates repositioning to gain good bed coverage.
- The spray rate per gun on the production scale can be substantially higher, requiring that the guns be moved further away to prevent localized overwetting.

Clearly, therefore, greater attention should be paid to how spray guns are set up. In reality, unless spray gun positioning is optimized during process development, the same type of guns are to be used in both the laboratory and the manufacturing plant, and the spray rate per gun can be maintained (within reasonable ranges) in both cases, it is futile to expect to be able to fix gun-to-bed distances no matter the scale of process used. Even so, greater consideration should be given to achieving these ideals.

Pragmatically, therefore, it is quite normal to find that gun-to-bed distances will be 50–60% greater on the production scale than those used

on the typical laboratory scale (for a 24″, or 60 cm, diameter coating pan holding 10–15 kg of tablets).

Spray rate: Assuming there are no major climatic differences to be faced during technology transfer, then predicting typical spray rates to be adopted during scale-up is a relatively simple task. As a simple guideline, calculations should be based on the relative airflows used for each scale of process, as shown in Equation (1).

$$S_2 = (S_1 \times V_2)/V_1 \tag{1}$$

where S_1 is the spray rate used on the scale used in process development, V_1 is the air volume used on the scale used in process development, V_2 is the air volume used on the larger-scale process, and S_2 is a prediction for the spray rate to be used.

If substantial changes in other parameters are expected (environmental humidity, processing temperatures as a result of heater capabilities, etc.), then better predictions can be made using the thermodynamic principles outlined in the section, "Thermodynamics of the Film-Coating Process."

For a side-vented pan-coating process, the processing data shown in Table 7 exemplify some spray rates that may well be used during process scale-up. It is interesting to note from these data that the drying (and

Table 7 Example of Operating Parameter Ranges Used When Scaling-Up an Aqueous Film-Coating Process

	Pan type (and size or model)					
	Accela-Cota			Hi-Coater		
Parameter	24″	48″	60″	HCT 60	HC 130	HC 170
Inlet-air volume[a]:						
(a) cfm	250	1800	3800	260	900	1300
(b) m^3/hr	440	3200	6700	450	1600	2300
Exhaust air volume[a]:						
(a) cfm	300	2000	4000	280	1300	2100
(b) m^3/hr	525	3500	7000	500	2300	3700
Inlet temperature (°C)	60–80	60–80	60–80	60–80	60–80	60–80
Exhaust temperature (°C)	40–45	40–45	40–45	40–45	40–45	40–45
Spray rate (g/min)	40–70	250–500	500–1000	40–70	300–600	500–900
Pan speed (rpm)	12–14	4–7	3–6	12–14	4–7	3–6

[a]These are nominal air volumes, since actual values may be different depending on the installation and on whether the coating pan vendor or an independent supplier supplied the air handling equipment.

exhaust) air volumes used in the production-scale Hi-Coaters are somewhat lower than those seen in an equivalent scale Accela-Cota, or, indeed, as might be predicted from studies conducted in a laboratory-scale Hi-Coater. These differences reflect design considerations that suggest that, in the Hi-Coater, incoming air has essentially no place to go except out through the exhaust plenum and thus must pass through the coating pan (and therefore the tablet bed). In other types of side-vented coating pans, particularly those that are completely perforated, incoming air is often introduced into a cabinet that surrounds the outside of the coating pan itself, and must pass through the perforated section of the pan in order to gain access to the inside the pan (and thus effectively dry the tablets). As a consequence, fully perforated pans are often operated with higher drying air volumes. These different requirements do not pose any problems unless a pharmaceutical manufacturer decides to switch from one type of coating pan to another and contracts with an independent vendor to provide the air-handling equipment. In this situation, it is critical that recommended specifications (from the coating pan vendor) should be obtained in order to ensure that the independent contractor provides an appropriately sized system.

These idiosyncrasies, in terms of airflow requirements, do complicate matters, however, when scaling-up from one type of coating pan to another. These complications arise when applying the simple predictions (based on Equation 1) for spray rates. If the scale-up process involves switching from a laboratory-scale fully perforated pan to a production-scale Hi-Coater, there is a risk that the predicted spray rates will be understated. For the sake of the calculation, a useful ''rule of thumb'' is to *double* the value for the actual air volume that will be employed in the larger-scale Hi-Coater, and to use that value solely for the purposes of the calculation.

Spray gun dynamics: Earlier in this section, frequent reference was made to the importance of establishing spraying conditions that are consistent from the development scale right up to that used in the manufacturing plant. Similarly, mention was also made of the scant attention typically paid to spraying dynamics and the lack of a strong understanding of what actually happens when droplets of coating fluid emerge from a nozzle, move towards the tablet bed, and impinge upon the surfaces of tablets.

All too often, an overly simplistic view is taken of the role that spray gun design (namely, brand of gun, and features of the fluid nozzles and air caps used) can play in achieving good, and reproducible, coated tablet quality. The fact that spray gun design may differ (from laboratory to production setting) is often considered to have little relevance, and accommodations for such differences are routinely made based on prior experience and, often, instinct, without benefit of reference to scientific data. A commonly held assumption, therefore, is that guns made by one manufacturer are

essentially the same in terms of gun performance as those from another, and differences that exist are purely in the features presented and, ultimately, the cost.

Quality attributes of film-coated tablets that can be associated with spray-gun performance include:

- Appearance
  - coating gloss
  - coating roughness
  - existence of defects (''picking,'' edge chipping/edgewear, filling in of logos)
  - color uniformity
- Functional
  - uniformity of distribution of coating
  - coating porosity (which influences film permeability)
  - solvent (water) penetration into the tablet cores, and hence product stability

Clearly, there is thus a great incentive to gain a better understanding of those factors that influence gun performance, as well as those differences that exist between guns supplied from different manufacturers.

In a recent presentation, Cunningham (12) has described some of the factors that can influence spray gun performance and has compared the performance of spray guns from different vendors. As can be seen from the results shown in Figure 7 (where the performance of a Schlick spray gun is compared to a Spraying Systems spray gun), the influence of gun-to-bed distance and coating suspension solids content on mean droplet size is quite different for each type of spray gun. In both cases, droplet size tends to increase the further away from the nozzle one goes (probably due to droplet collisions, causing size enlargement). The influence of coating suspension solids content on mean droplet size is much more pronounced, however, in the case of the Schlick gun (producing results in the range of approximately 25–275 μm), compared to the Spraying Systems gun, which yields droplet sizes in the range of 30–60 μm under the same conditions. These results clearly have implications for situations where the type of gun may be changed on scale-up, but also where gun-to-bed distance may also be changed in the same process. Comparing the data shown in Figure 8, the differences are even more pronounced when observing the influences of spray rate and atomizing air pressure on mean droplet size. Since these two parameters are commonly increased during the scale-up process, it can clearly be seen that little change would occur when using a Schlick gun, but the change would, indeed, be substantial if a Spraying Systems VAU gun was used.

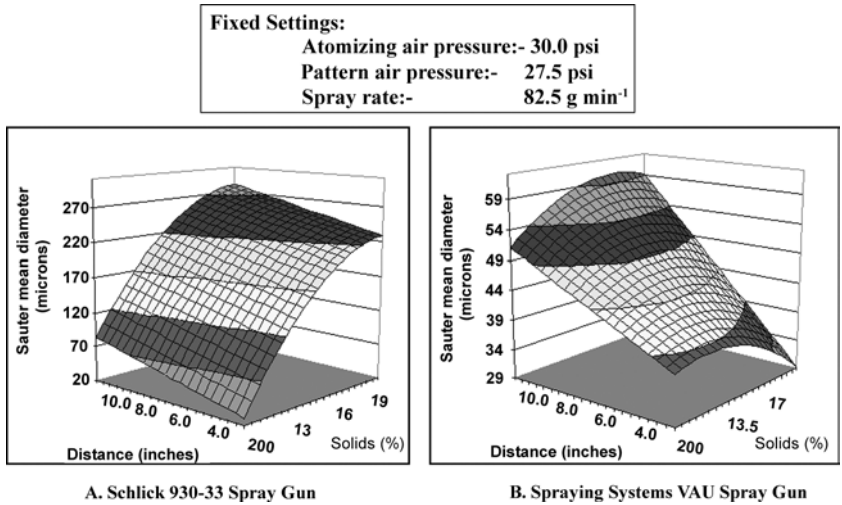

Figure 7 Example of how the type of spray gun used, gun-to-bed distance, and solids content of the coating fluid can influence the size of droplets generated.

An argument might be made that, when coating tablets, such changes in mean droplet may be of no consequence, since the ranges of droplet sizes achieved are still quite small when compared to that of the tablets being coated. This viewpoint is overly simplistic, since the size of droplets formed

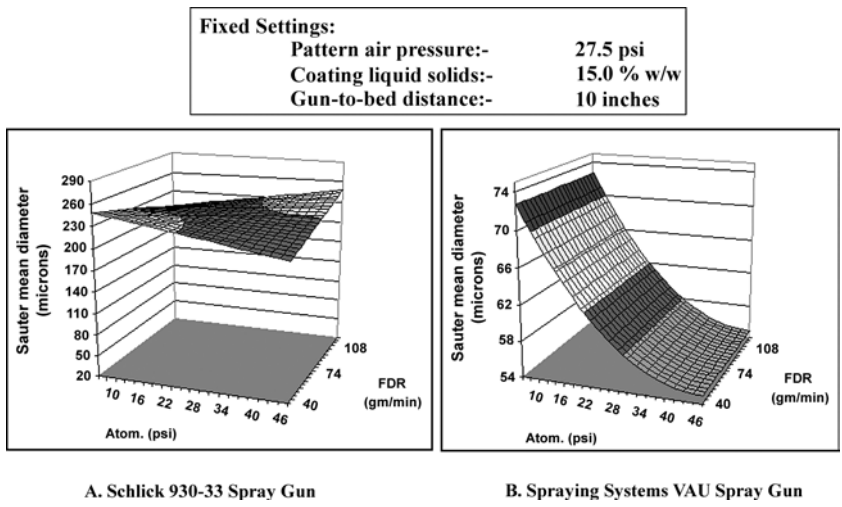

Figure 8 Example of how the type of spray gun used, atomizing air pressure, and spray rate can influence the size of droplets generated.

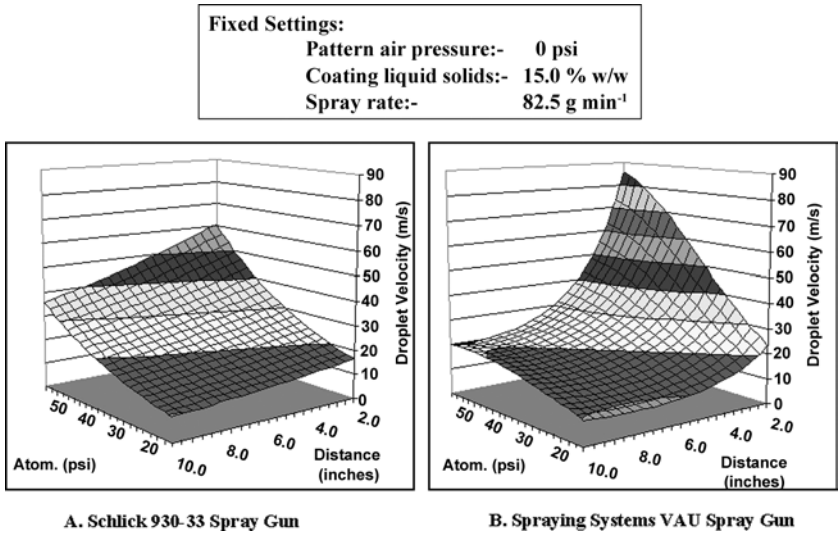
Fixed Settings:
Pattern air pressure:- 0 psi
Coating liquid solids:- 15.0 % w/w
Spray rate:- 82.5 g min-1
Droplet Velocity (m/s)
Atom. (psi)
Distance (inches)
A. Schlick 930-33 Spray Gun
B. Spraying Systems VAU Spray Gun

Figure 9 Example of how the type of spray gun used, atomizing air pressure, and gun-to-bed distance can influence droplet velocity.

can have an influence on coating smoothness and gloss, as well an impact on how rapidly the liquid dries during flight from the spray nozzle to the tablet surface.

Further comparisons between these two types of spray guns indicate that there are differences in droplet velocity produced (Fig. 9), as well as the breadth of coverage on the surface of the tablet (Fig. 10).

Droplet velocity, especially for those droplets arriving at the tablet surface, can potentially influence:

- wetting (velocity at impact can influence the advancing contact angle formed between the tablet surface and the droplet, and the degree to which the droplet spreads immediately after contact) and, ultimately, film adhesion
- overspray, where the velocity of impact may cause droplets to be reflected from the tablet surface

The breadth of coverage can influence the number of spray guns that will be needed and the likelihood that overspray onto the sidewalls of the pan will occur. Clearly the results shown in Figure 10 suggest that fewer spray guns of the Schlick type will be required to give equivalent coverage to that obtained when using Spraying Systems guns.

In summary, the results shown in Figures 7–10, which only represent data for two distinct types of spray guns, provide clear warning of the potential problems that can occur if, during the scale-up process, commonly seen

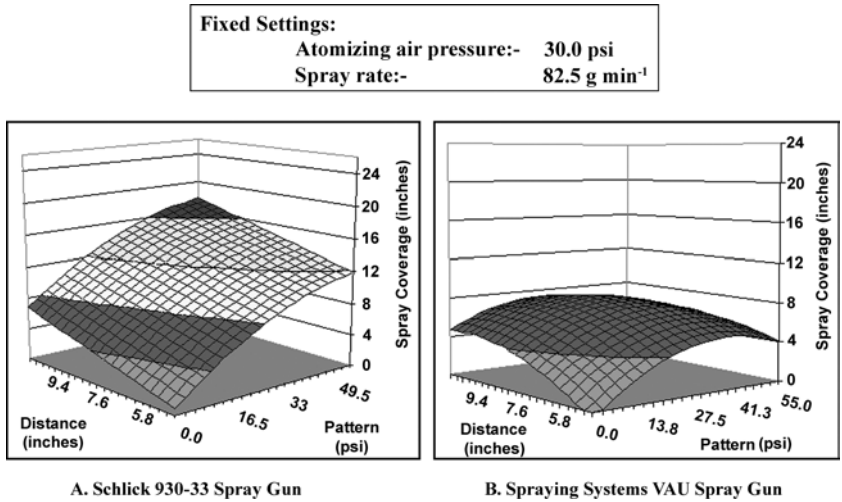

Figure 10 Example of how the type of spray gun used, gun-to-bed distance, and pattern air pressure can influence bed coverage.

differences in spray-gun performance are ignored. Appreciation for this situation is of paramount importance when one considers that there is a very real possibility that the types of spray guns used may be changed, especially if scale-up involves technology transfer from a development site to a manufacturing one that is geographically remote, quite a common occurrence in these days of globalization.

Scale-Up of Pan-Coating Processes: A Case Study

From the foregoing discussion, there are clearly many issues to be confronted when scaling up the pan-coating process. Evidently, the more definitive data that are developed initially, the less likely that major problems will occur later on, especially problems that could inevitably delay a product launch and cost much in the way of lost revenues, particularly when dealing with a potentially "blockbuster" drug product.

This case study will summarize the development of a pan-coating process designed for the application of an enteric coating to a tablet product, provide insight into some of the early process optimization studies that were undertaken, and show how these ultimately facilitated the development of production-scale manufacturing processes.

Initial process development: Early development studies were carried out using a laboratory-scale 24″ Accela-Cota and employing a statistical design of experiments technique in which the operational variables were as shown in Table 8. Although several response variables were examined

Table 8 Ranges of Process Variables Used During Optimization of the Enteric Film-Coating Process

Parameter studied	Ranges examined
Solids content of coating suspension (based on Sureteric® YAE-6-18108) (% w/w)	10–25
Inlet-air temperature (°C)	50–70
Spray rate (g/min)	50–90
Quantity of coating applied (% w/w)	5–10
Atomizing air pressure (psi)	25–55
Atomizing air pressure (bar)	1.75–3.75

in this study, the principal issues were concerned with providing good functional enteric performance. Recognizing that enteric products are often potentially known for their lack of robustness (manifested as inherent brittleness of the coating which is likely to cause enteric failures during subsequent handling, such as emptying the coating pan, printing, packaging, etc.), an extra challenge was imposed in the form of a *stress test* (see later discussion) to confirm appropriate robustness of the final dosage form. The two criteria used to measure enteric performance, therefore, were:

- *Enteric Test* (*ET*): A hundred tablets were exposed to artificial gastric juice (0.1 N hydrochloric acid solution) for two hours, using a modified disintegration tester. Performance was expressed in terms of *percent failure*, which was represented by the percentage of tablets showing any sign of enteric failure (such as premature disintegration, swelling, or even slight softening).
- *Stressed Enteric Test* (*SET*): Essentially the same test as the Enteric Test (ET), but in this case, the 100 tablets were placed in a friability tester for four minutes at 25 rpm prior to being submitted for the enteric disintegration test in artificial gastric juice.

From this initial study, and referring to the data shown in Figure 11, it is evident that good functional enteric performance can be achieved when the coating process is operated under conditions where;

- the inlet-air temperature is greater than 60°C, and
- the coating suspension solids content is in the range of 10–15% w/w.

The data represented by the stressed enteric results (SET), however, tell a slightly different story (Fig. 12A). Clearly, the process operating ranges where acceptable performance can be achieved are quite limited. However, if the level of applied enteric coating is fixed at a minimum of 10% w/w, and the coating suspension solids content is reduced to 15% w/w, then the process operating ranges become quite broad (Fig. 12B).

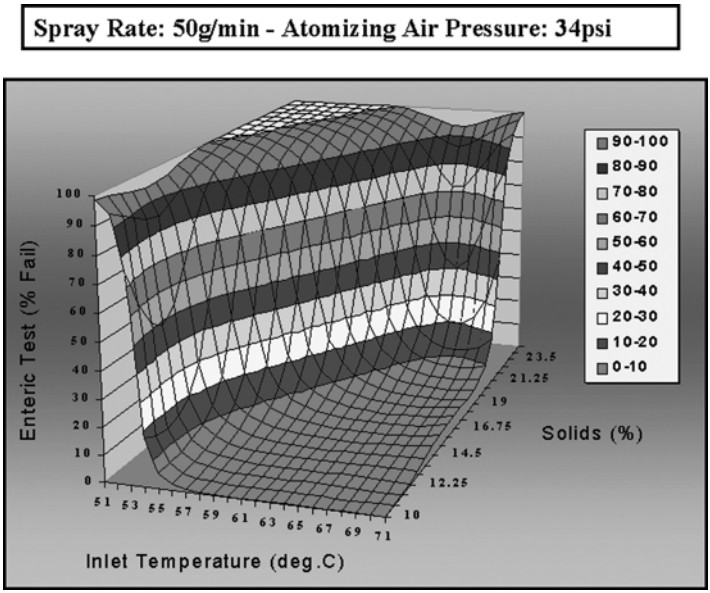

Figure 11 Influence of inlet-air temperature and solids content of the coating suspension on enteric test performance of enteric-coated tablets.

Scaling-up the optimized enteric-coating process: Based on the results described in the previous section, an optimized coating procedure was designed and used as a platform for scaling-up the enteric-coating process. Details of this optimized laboratory process, as well as the conditions used

A. Spray Rate:	50 g/min
Suspension Solids:	17.5%w/w
Atomizing Air Pressure:	34 psi

B. Coating Level:	10 %w/w
Suspension Solids:	15 %w/w
Atomizing Air Pressure:	34 psi

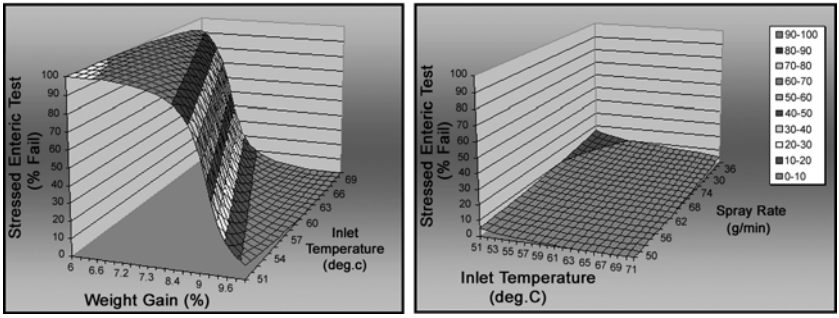

Figure 12 Example of how process conditions can influence the enteric performance of tablets that have been submitted to a stress test prior to undertaking the enteric test.

in the scale-up study, are shown in Table 9. In addition, the results for the enteric tests performed on tablets coated in these coating trials are shown in Table 10.

The fact that these results clearly meet (and in most cases, surpass) the specifications designated for the enteric testing of aspirin tablets provides sufficient confirmation for the validity of the optimization and scale-up procedures used in this case study.

Table 9 Coating Process Details Used in Scaling-Up an Aqueous Enteric-Coating Process Using an Accela-Cota Process

	Coating process conditions for scale indicated		
Process parameter	24″ Accela-Cota	48″ Accela-Cota	60″ Accela-Cota
Inlet-air volume:			
(cfm)	250	1800–2000	2300–2700
(m^3/hr)	425	3100–3400	3900–4600
Exhaust air volume:			
(cfm)	300	1900–2100	2400–2800
(m^3/hr)	500	3200–3600	4100–4800
Inlet-air temperature (°C)	75–84	70–80	70–80
Exhaust-air temperature (°C)	38–41	40–45	40–45
Spray rate (g/min)	60–70	400–500	650–700
Number of spray guns (Binks 605; fluid nozzle 66SS; air cap 66SH)	2	3	5
Gun-tablet-bed distance:			
(inches)	5–7	8–12	10–12
(cm)	12–18	20–30	25–30
Atomizing air pressure:			
(psi)	35–40	60–80	50–70
(bar)	2.4–2.7	4.1–5.5	3.5–4.8
Pan loading (kg) of Aspirin 325 mg tablets	12.0	135	300
Tablet bed prewarm temperature (°C)	45–50	45–48	45–48
Pan speed (rpm)	14	6	4
Enteric-coating suspension solids content (% w/w)	15.0	15.0	15.0
Quantity of coating applied (% w/w)[a]	10.0	10.0	10.0
Coating process time (hr)[a]	2.00	3.00–3.75	4.75–5.10

[a]This only refers to the enteric-coating layer; in addition, a subcoating (based on Opadry) applied to a level of 2.0% w/w, and a colored top coating based on Opadry II applied to a level of 3.0% w/w were also used.

Table 10 Enteric Test Results for Aspirin (325 mg) Tablets Coated in Scale-Up Processing Studies

	Disintegration test			Dissolution test	
	% Failures in 0.1 N HCl solution				
Batch size (kg)	Enteric test (ET)	Stressed enteric test (SET)	Disintegration time in buffer, pH = 6.8	% Drug released after 2 hr in 0.1 N HCl[a]	% Drug released after 90 min in buffer, pH = 6.8[a]
12	0	0	8:05 ± 0:32	0	104.5
135	0	0	7:04 ± 0:52	0	91.5
300	0	0	6:32 ± 1:00	0	105.2

[a]Compendial specification calls for: <10% dissolved in 0.1 N HCl after 2 hours and ≥80% dissolved in buffer, pH = 6.8, after 90 minutes.

Table 11 Features and Uses of the Three Concepts for Fluid-Bed Film Coating

Process	Advantages	Disadvantages	Uses
Top spray	Larger batches Easy nozzle access Relatively simple setup Good mixing	Limited batch weight flexibility Limited weight gains Greater risk of spray drying	*Application of*: Aqueous coatings Taste mask coatings Hot-melt coatings
Bottom spray	Moderate batch sizes Uniform distribution of coatings Wide range of applications	Poor nozzle access during coating Requires tallest expansion chamber	*Application of*: Aqueous coatings Taste mask coatings Modified-release coatings Drug-layer coatings
Tangential spray	Relatively easy setup Easy nozzle access Shortest processing chamber Fast spray rates Wide batch weight flexibility	High mechanical stress on product being coated	*Application of*: Drug-layer coatings Modified-release coatings

Scaling-Up Fluid-Bed Coating Processes

Introduction

Fluid-bed coating processes, although applicable for coating the full range of pharmaceutical product types, are more likely to be reserved for the coating of multiparticulates, usually with some kind of functional coating (taste masking, enteric, and sustained release). The nature of the substrate and the purpose of the applied coating clearly provide additional challenges during both initial process development and the scale-up process. This situation is made even more complex by the fact that with the current preference for aqueous coating formulations, such highly functional coatings often demand the use of latex or polymer dispersion coating systems. These systems have certain idiosyncrasies in terms of film formation that place extra demands when optimizing the coating process in order to ensure that stable, reproducible applied coatings are obtained.

Much has been said in the discussion so far as it relates to scaling-up the pan-coating processes. Philosophically, many of the issues already described are equally applicable to the fluid-bed process. There are, however, some important differences that must be appreciated during the development of fluid-bed coating processes. For the most part, although there is a plethora of pan-coating equipment currently available, and each brand has its specific characteristics and features, the operating principles are essentially the same for most types of equipment that are in common usage in the pharmaceutical industry today. In contrast, when it comes to fluid-bed coating, there are three distinct processing concepts commonly used, as illustrated in Figure 2. To summarize, these are:

- the *top-spray* process, which is a manifestation of the fluid-bed granulation process that has long been used in the pharmaceutical industry
- the *bottom-spray* process, commonly called the *Wurster* process and the only one that was specifically designed as a coating process
- the *tangential-spray*, or *rotor*, process, originally designed as a granulator for producing spheronized granulates

Each of these processing concepts, which can all be supplied by each of the major vendors of fluid-bed coating equipment, has special characteristics that make it suitable for certain tasks, as shown in Table 11. Although the concepts outlined in this table represent those that are frequently used in the industry today, some specialized fluid-bed processes, the operating principles of which fall outside those of the three listed, are also worthy of note. Examples would be the "Kugelcoater" (which is manufactured by BWI Manesty in Europe), and the "Precision Coater" (manufactured by GEA).

In contrast to pan-coating processes, some characteristics of fluid-bed processes that may feature strongly in the scale-up process include the fact that:

- Nozzle positions (with the possible exception of the top-spray process) are somewhat fixed, and the distances between the nozzle tips and product being coated are often quite small and unlikely to change on scale-up.
- Spray patterns are always round, and thus pattern air is not a factor in the atomizing process or in defining the spray characteristics.
- Although fluid-bed machines have optimal operating capacities, they often have much more flexibility in accommodating a range of batch sizes within a given process, especially those based on the tangential-spray concept. Although there is a certain minimum requirement in order to facilitate appropriate fluidization of the product, this flexibility is often a requirement when one considers that the amount of coating material that is often applied may range from 1% to 50% (and even broader if one includes the drug-layering process). Such extremes are rarely required in typical pan-coating operations.
- Nozzle (atomizing) air can contribute significantly to product movement and can also be a source of a significant increase in product attrition.
- Drying air is also the main source of "power" for creating product movement. Thus, the needs of the drying process and that required to create motion are interdependent, adding complexity in terms of meeting (and optimizing) the requirements of each. For example, when a significant amount of coating material is being applied, the batch mass will increase, requiring more air volume to maintain motion; at the same time, the requirements for drying remain little changed.

Predicting Scale-Up Issues

As with pan coating, the key to successfully scaling-up the fluid-bed process involves the design of a completely optimized laboratory-scale process on which key decisions can be based. As discussed earlier, Turkoglu and Sakr (8) have provided an appropriately relevant example of how such an optimized fluid-bed process (in this case, a tangential-spray process) may be designed. It is not unexpected to assume that certain features of the process will again remain unchanged throughout the scale-up process. These features include:

- product and coating formulations
- solids content of the coating liquid
- inlet-air and product temperatures (although these may be adjusted to accommodate other limitations that may arise, such as uncontrollable changes in drying air humidity and limitations on heater capacity)

Key processing parameters on which much attention will have to be focused include primarily:

- Batch size
- Drying/fluidizing air volumes
- Spray nozzle dynamics
- Spray/evaporation rate

The photographs shown in Figure 13 provide a useful example of the kinds of equipment changes that can take place when scaling-up a fluid-bed process. In this case, reference is made to the Wurster process, which possesses some useful characteristics to determine that, once the pilot scale (in this case, the 18″ Wurster process) is reached, larger machines are based on multiples of the 18″ concept, thus somewhat simplifying further scale-up. Thus, with this type of process, many of the challenges occur when scaling-up from the laboratory to pilot scale, rather than from pilot to full production scale.

Considerations for batch size: Mention was made earlier in this chapter, and much has been said in pharmaceutical publications, about the

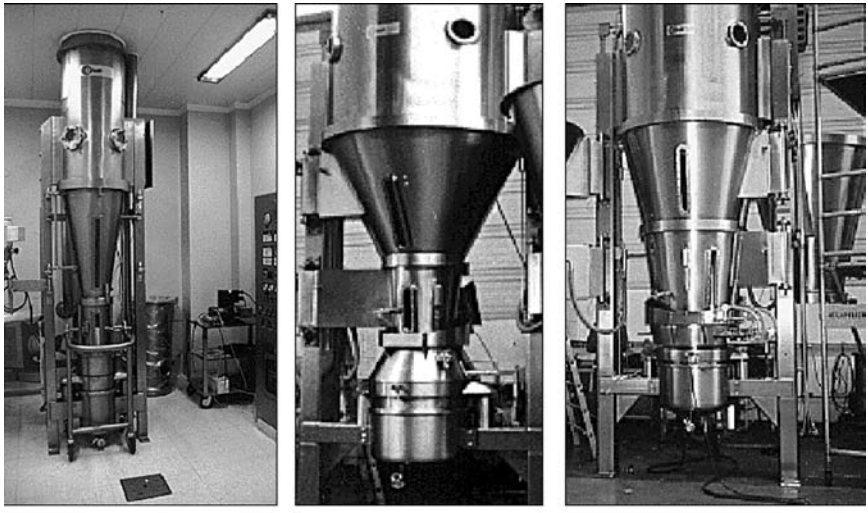

Figure 13 Photographs illustrating equipment used during the scale-up of the Wurster process.

batch-size flexibility that is often associated with the fluid-bed process. It is perhaps more appropriate, however, to talk in terms of the flexibility of such equipment to accommodate ranges in starting batch weight. Any fluid-bed process that is involved in a coating application will always have an optimum batch fill weight that, as with pan-coating processes, will be defined by the interior volume of that particular machine. Each will also have an upper capacity limit that is defined by the operating needs of that process.

It is critical, during initial process development, to give serious consideration to the amount of material that will be applied (especially for processes involving drug layering or those involved with the application of modified-release coatings to fine particle products, where required coating levels in excess of 50% are not uncommon). Key factors to be established are:

- What are the minimum and maximum limits for batch capacity in a particular machine?
- How much coating material is to be applied?

Answering these questions provides suitable guidelines for deciding on which particular type of process is appropriate. Selection of the wrong process may require that, part way through processing, the batch may have to be divided in order to allow the full process to be completed. Such a necessity is more likely when using the bottom-spray (Wurster) process and least likely when using the tangential-spray process. Dividing batches in this manner is rarely troublesome on the laboratory scale but becomes much more of a issue when going to large production-scale processes, which is something that may prove to be a potentially costly oversight during the initial stages of process development.

Since batch size constraints may be more significant in the Wurster process, this processing concept will be used primarily as the basis for further discussion on the subject of defining appropriate batch sizes.

For fluid-bed processes, a useful limit to consider is *working capacity*, which essentially refers to the final batch weight. In the case of the Wurster process, this term refers to the volume *outside* the inner partitions. The minimum starting batch size for the Wurster process is usually approximately 40% of its working capacity. This loading is essentially a guideline, since a critical element of this process is to ensure that there will ultimately be enough material in the *up bed region* (that is, inside the partition(s) when the process is in operation) to capture all of the material that is being sprayed, so avoiding low process coating efficiencies as a result of material that will either be deposited on the side walls of the inner partition(s), or material that will not be captured by the product being coated and will pass all the way up into the filter system. Using the 40% guideline is only suitable when the amount of coating (or drug to be layered) is substantial. When the coating level is low (less than 10% w/w), then the starting batch weight should be more in the range of 60–70% of working capacity.

For the Wurster process, calculating batch volume on scale-up can be calculated using Equation (2)

$$B = \frac{\pi {r_1}^2 L - n\left(\pi {r_2}^2 L\right)}{1000} \tag{2}$$

where B is the batch volume, or working capacity (liters), r_1 is the radius of the product (Wurster) chamber (cm), r_2 is the radius of each inner partition (cm), n the number of inner partitions, and L is the length of each inner partition (cm).

If the batch volume is multiplied by the bulk density of the product to be coated, then the batch load, by weight, can be determined.

Although these examples are more specific to the Wurster process, similar guidelines can be applied to the top-spray process, although, in that case, the definition for working capacity will be different. When dealing with the tangential-spray process, the quantity of product that is sufficient to ensure that the spray nozzles are completely immersed when the product is in motion will define the minimum starting batch weight.

Drying/fluidizing air volumes: As stated earlier, unlike the case of a coating pan, the air that passes through a fluid-bed machine serves two purposes, namely, drying and imparting motion. The key objectives in each case need not be mutually inclusive. Keeping the product moving in an appropriate manner, and the volume of air required to do that, may well depend on:

- the mass of material inside the machine. This requirement is confounded by the fact that as more coating is applied, the mass increases, as does the requirement for fluidizing air, and
- the tackiness of the coating being applied. Tacky coatings can increase both the "drag" on coated particles and also the potential for agglomeration to occur. In either case, an increase in fluidizing air may well be required to offset these two problems. Tackiness is often associated with the nature of the polymer(s) used in the coating system, the presence of other additives (such as plasticizers), excessive levels of residual solvents present as a result of ineffective drying, and, especially with the use of latex coating systems. When ineffective drying is the cause of tackiness, an increase in air volume may be a suitable remedy. When this problem is caused by the other factors, an increase in airflow may act as a double-edged sword; increasing airflow, by improving motion, may well alleviate the problem; however, increased airflow, by increasing the level of heat in the product, may well result in increased tackiness.

In each of these scenarios, while a change in airflow will presumably improve product movement, unless spray rates (or process temperatures)

are changed appropriately, the associated increase in drying capacity may well be detrimental to the process.

In general terms, the top- and tangential-spray processes may be less demanding in their requirements with respect to airflow. In the former, the fluidization pattern is quite random; in the latter, much of the burden for creating motion falls on the spinning disk, so that the incoming air is required only to:

- create lift at the walls of the processing chamber
- prevent product from dropping below the spinning disk
- facilitate drying

Again, it is the Wurster process that presents the greatest challenge in optimizing airflows, where it is desirable to ensure that product rapidly accelerates up through the inner partition while maintaining a smooth, even flow in the down bed (and essentially maintaining product in the down bed in a near-weightless condition). Considering the range in particle sizes of the products that may be coated in this process, some accommodation can be made in terms of specific product requirements by changing the orifice plate (which determines the relative amounts of air passing upward through the region of the inner partition(s) and also that meeting the downward moving product in the down-bed region of the processing chamber) at the bottom of the processing chamber, as well as the relative height of the inner partition.

When scaling-up the fluid-bed process, a major requirement is to produce fluidization behavior on the larger machines equivalent to that used on the scale that provided the basis for process development. To achieve this goal, and minimize attritional effects, the same air velocities for each scale of equipment are required. Thus, the overall increase in air volume required during scale-up will be related to the increase in area of the perforated base plate, and, in the case of the Wurster process, the open area of the partition plate immediately beneath each of the inner partitions. Such calculations are simplified when scaling-up from an 18″ pilot scale machine to, say, a 32″ machine, since the latter represents a three-multiple of the former, and thus would require a threefold increase in airflow.

Spray nozzle dynamics: Spray nozzle dynamics often prove to be a more challenging subject when dealing with fluid-bed processes, because:

- often the product being coated is a multiparticulate ranging in size from approximately 50 μm up to about 2–3 mm in size
- in order to coat each particle in a discrete manner and avoid agglomeration, the coating fluid must often be atomized more finely, and in a more controlled manner, than in the case where tablets are coated in a typical pan process
- in order to maintain fineness of atomization at the higher spray rates typically required in the larger-scale processes, atomizing

air pressures may often have to be increased to levels where atomization air velocity can seriously increase product attrition
- in order to meet the atomization constraints required, it is almost always necessary to change the model of spray gun used in order to achieve the effective levels of atomization at the increased spray rates required during the scale-up process

With the possible exception of the top-spray process, the issues of nozzle-to-bed differences become a non-issue in the fluid-bed process, since this distance is extremely small and, to all intents and purposes, fixed. Indeed, the close proximity between the nozzle and the product being coated can be problematic in some cases, since the velocity gradient created between the fluidizing air and the atomizing air can cause product to be drawn into the wettest part of the spray, increasing the chances of localized overwetting and agglomeration.

As a result of the substantial interest in use of aqueous coating systems, an added burden is placed on the atomizing process. This burden results from the relatively high viscosities and surface tensions of aqueous systems. Fortunately, in applications using modified-release coatings, aqueous versions of such coating systems are typically in the form of latexes, or polymer dispersions, which have relatively low viscosities for the solids content of the coating system, and the presence of surfactants (as dispersion stabilizers) facilitates a reduction in what would otherwise be high surface tension values.

The data displayed in Figure 14 clearly indicate the dilemma with which one is faced when trying to achieve an increase in spray rate for a given type of nozzle. In the examples shown, the Schlick 970 series gun is typical of what is used on the laboratory scale, while the 940 series gun is more suitable for pilot- and production-scale operations. Clearly, the 940 series gun has serious limitations when scaling-up to full production requirements, since if, for example, it is desirable to achieve a mean droplet size of 15 μm, this objective can be achieved (by increasing the atomizing air pressure as spray rate is increased) as long as the required spray rate does not exceed 250 mL/min. For all practical purposes, 6 bar represents a practical upper limit for atomizing air pressure in this type of coating process in order to prevent serious product damage due to attrition. Under these circumstances, if effective atomization cannot be achieved, use of specialized nozzle set-ups, such as those employed in the Glatt HS system, offers a potential solution. These types of nozzle allow higher spray rates to be achieved (Fig. 15) since:

- the higher atomizing air velocities produce smaller droplets, even at high spray rates
- a special nozzle surround keeps product further away from the nozzle tip, thus preventing that product from being drawn into the "wet" area of the spray zone, and also limits the attritional

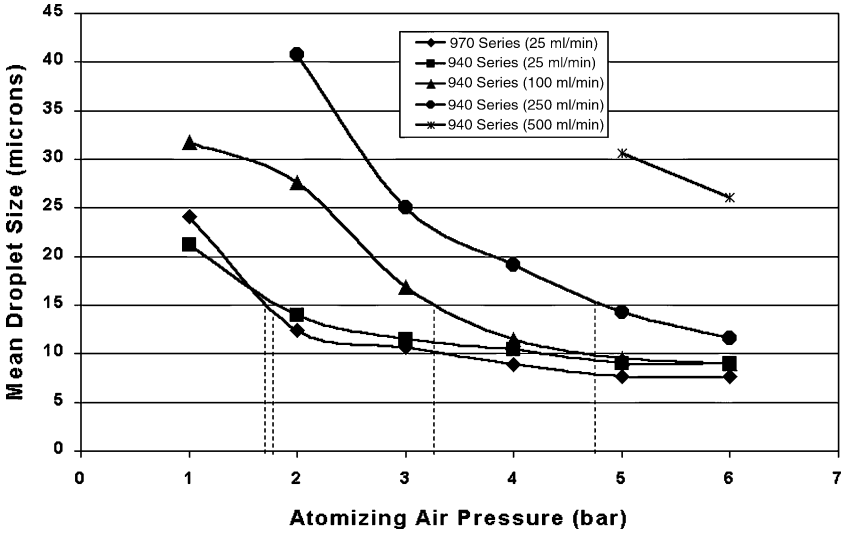

Figure 14 Influence of spray nozzle type and atomizing air pressure on the mean droplet size of water sprayed from guns used in a Wurster process.

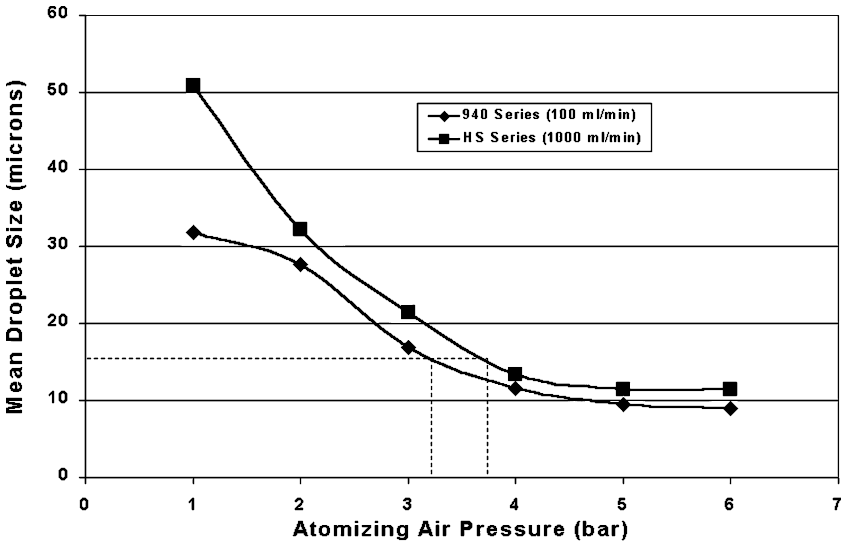

Figure 15 Example showing how a highly specialized nozzle (HS nozzle) can achieve equivalent atomization at high spray rates to that obtained by a more conventional nozzle when used at lower spray rates.

effects that normally accompany the use of high atomizing air pressures and velocities

Spray/evaporation rate: As described when discussing scaling-up the spray application rates used in pan-coating operations, application of simple models (as represented by Equation 1) can prove to be extremely useful also for fluid-bed processes. Further refinements, in terms of fully optimizing the process in this regard, can be achieved by applying appropriate thermodynamic principles. Jones (13) has provided a good example of how such an approach can be applied to a fluid-bed coating process.

The spray rate that can be achieved in a given process is related to the volume of air that passes through the machine, and the temperature and humidity of that air. Clearly, therefore, spray rate will be governed to some extent by the rate at which the solvent (aqueous or otherwise) can be removed. Spray rate will also be influenced by:

- the behavior of the coating fluid,
- the inherent tackiness of the coating, especially during the critical time immediately after deposition onto the surface of the substrate, and
- the rate at which the product being coated moves through the spray zone. Generally, the faster that product moves through the spray zone, the lower is the "dwell time," and the less coating that is captured during that time, resulting in a faster dry time for the coating. As the rate at which the applied coating dries (so that particle-to-particle contact no longer carries the risk of interparticulate adhesion, resulting in agglomeration) has an direct influence on the ultimate spray rate that can be achieved, rapid particle movement through the spray zone increases the potential to spray faster.

Summary of scale-up issues: Scaling-up the fluid-bed process clearly faces many hurdles that are both similar and, at the same time, different from those faced with pan-coating processes. Additional complexity stems from the nature of the substrate that is likely to be coated in the fluid-bed process, as well as the fact that, very often, the applied coating has a very important role to play in drug delivery.

That said, the task should not be overcomplicated, and many good instances exist to illustrate successful conclusions to such efforts. For example, the data shown in Table 12 illustrate the scaling-up of the Wurster process in which an aqueous latex coating has been applied to drug-loaded pellets in order to prepare a modified-release product. It is appropriate to point out that since the 32″ Wurster essentially comprises three 18″ Wurster units, the airflow used in the former represents approximately a threefold increase over that of the latter, with the result that the spray rate is scaled

Table 12 Coating Process Conditions Used in the Scaling-Up of the Wurster Process for Application of an Aqueous Latex Coating to Drug Loaded Pellets

	Process parameter settings		
Process parameter	7″ Wurster	18″ Wurster	32″ Wurster
Inlet temperature (°C)	70	70	64
Inlet dew point (°C)	20	15	11
Product temperature (°C)	34	34	33
Fluidizing air volume (m^3/hr)	270	1225	3740
Atomizing air pressure (bar)	2.0	2.0	3.0
Spray rate (g/min)	50	300	850
Exit air R.H. (%)	85.4	73.7	64.5
Yield (5%)	99.0	96.7	98.4

up by the same factor. This situation illustrates the relative simplicity of scaling-up from the pilot-scale unit.

The functional characteristics (in terms of drug release) for the pellets coated in this particular study are shown in Figure 16. Statistical comparison of these data (using the f_2 factor) confirms that these drug release profiles are essentially equivalent, although the best comparison, as is evident

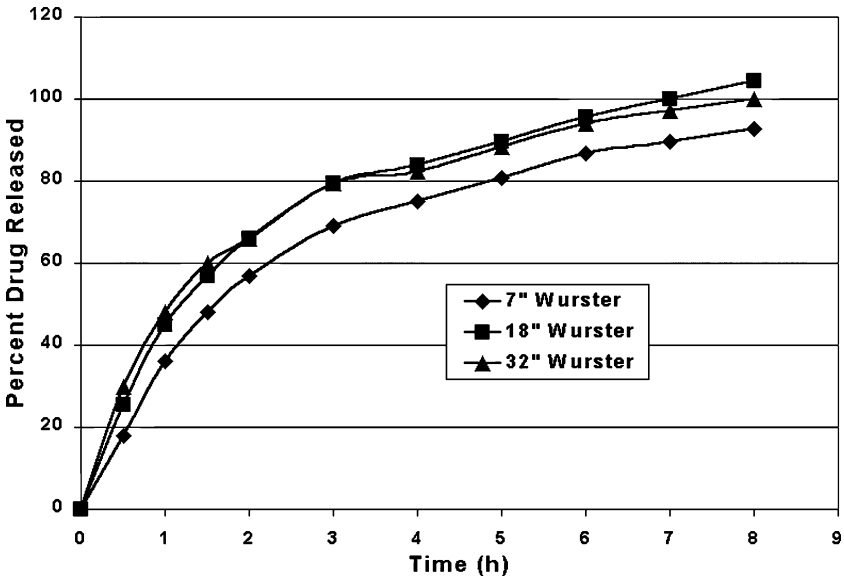

Figure 16 Comparison of drug release characteristics of pellets coated with an aqueous ethylcellulose dispersion using a laboratory-, pilot-, and production-scale Wurster process.

by simple visual inspection, is illustrated by the results for the coating trials performed on the pilot and production scales. This observation should not be all that surprising, since the processing conditions used in both these cases showed close agreement.

Scale-Up of Fluid-Bed Coating Processes: A Case Study

Effective product and process optimization play a prominent role in any successful scale-up study. As an illustration, this case study summarizes the initial development, and subsequent scale-up, of a Wurster process designed to facilitate the application of an aqueous ethylcellulose dispersion to drug-loaded pellets. At the same time, it was intended to deal, up front, with some of the idiosyncrasies of such a coating system that often influence the functionality of the final dosage form.

Initial process development: A preliminary study was established to examine the potential influence of processing parameters on some critical performance attributes of the final product, especially those associated with ultimate drug release rate, and the reproducibility of same.

Making certain assumptions about formulation issues (both with regard to the substrate being coated, and the coating system being applied), the ultimate influence of the applied coating on drug release rate can be reduced to two key elements, namely:

- the thickness of the coating applied
- the structure of that coating

Having fixed the amount of coating to be applied, and having controlled the surface area to be covered by selection of a specific size fraction of pellets to be coated, the one significant processing factor that can affect coating thickness is the relative coating efficiency achieved (i.e., the actual quantity of coating deposited relative to the theoretical amount applied). At the same time, coating structure will be influenced by:

- the effectiveness of coalescence of the latex coating
- the incidences of defects such as ''pick marks'' or ''cracks''

Consequently, in this study, the critical factors that were examined during process development involved establishing the influence of process conditions on:

- coating process efficiency
- coalescence of the film coating (determined by means of assessing drug-release characteristics before and after imposition of a ''curing'' step)
- evaluating the impact of processing conditions on film structure (by means of visual analysis, using scanning electron microscopy)

Table 13 Process Variables Used in the Development and Optimization of a Coating Process Designed for the Application of a Modified-Release Film Coating to Drug-Loaded Pellets

Process variable	Variable ranges evaluated
Solids content of aqueous ethylcellulose dispersion (% w/w)	10.0–25.0
Inlet-air temperature (°C)[a]	50–70
Spray rate (g/min)	15–45
Atomizing air pressure (bar)	1–3
Oven curing time at 60°C (hr)	0 or 24

[a]The fluidizing-air volume was adjusted during each run to maintain a constant fluidization pattern; the volume of air required to achieve this was recorded in each case.

Initial process development and ultimate process optimization were conducted as described by Vesey and Porter (14). Basically, the study was performed in a Glatt GPCG-3 unit fitted with a Wurster insert. The process variables that were evaluated are as shown in Table 13.

In order to assess the influence of process conditions on the coalescence efficiency of the latex coating, dissolution profiles (for samples from each coating run) were compared before and after being subjected to a curing step. Statistical analysis was undertaken using the f_2 fit factor, which is based on a logarithmic transformation of the sum of the squared error when comparing two dissolution profiles. The ultimate fit factor, expressed in terms of numerical values between 0 and 100, suggests that statistically equivalent dissolution profiles are achieved when the numeric values exceed 50.

A summary of the response variables obtained in this preliminary study are shown in Table 14, and the order ranking for the influence of process variables on the critical responses associated with coating process efficiency and drug release are provided in Table 15.

Table 14 Summary of Ranges Obtained for Response Variables Studied

Response variable	Variable ranges
Product temperature (°C)	22–58
Process air flow (m^3/hr)[a]	61–142
Coating process efficiency (%)	79.1–97.9
T_{50}, before curing (min)	75–340
T_{50}, after curing (min)	90–320
f_2 Value	56.6–95.6

[a]These ranges were used simply to maintain equivalent fluidization patterns for each coating run.

Table 15 Rank Order Summary of Process Variables Influencing Coating Process Efficiencies and Drug Release Characteristics (T_{50})

Coating process efficiency		Drug release (T_{50}) before curing		Drug release (T_{50}) after curing	
Variable	Ranking (%)	Variable	Ranking (%)	Variable	Ranking (%)
Inlet temperature	17	Spray rate	40	Spray rate	38
Spray rate × atomizing air pressure	17	Coating suspended solids	28	Inlet temperature × spray rate	21
Coating suspension solids	17	Inlet temperature	20	Coating suspension solids	19
Inlet temperature × spray rate	17	Atomizing air pressure	12	Inlet temperature	13
Spray rate × coating suspension solids	11			(Coating suspension solids)^2	9
Atomizing air pressure	11				
(Atomizing air pressure)^2	10				

As can be seen from the summary provided in Table 14, the processing conditions used clearly influence the ultimate drug release characteristics. On further examination, it was concluded that the major causes of the magnitude of differences in drug release characteristics were primarily due to:

- variation in coating process efficiency, which resulted in a significant variation in the actual amount of coating applied, and
- overwetting which occurred for the coating runs where product temperature fell substantially below those typically observed (38–42°C) for this type of process. Such overwetting induced a significant degree of drug leaching, as confirmed using elemental analysis employed during the application of scanning electron microscopy.

On the basis of the results obtained, an optimized procedure was designed which was intended to maximize both the coating process efficiencies and ensure that the f_2 fit factor values were in excess of 70.

Scaling-up the optimized process: Using the optimized coating process as a basis, procedures were developed which enabled the process to be scaled

Table 16 Details of Coating Procedures Used in Scaling-Up the Wurster Process

	Coating process conditions		
Process parameter used	Glatt GPCG-3	Glatt GPCG-60	Glatt GPCG-200
Batch size (kg)	3	70	200
Fluidizing-air volume (cfm)	83–107	800–900	N/A[a]
(m^3/hr)	140–180	1360–1530	
Inlet-air temperature (°C)	64–67	60–66	72–75
Exhaust-air temperature (°C)	40–45	39–41	47–51
Product temperature (°C)	41–47	40–46	43–46
Atomizing-air pressure (bar)	1.5	2.0	2.0
Number of nozzles used	One (Schlick 970, 1.2-mm orifice)	One (HS, 1.5-mm orifice)	Three (Schlick 940, 1.5-mm orifice)
Solids content of coating dispersion[b] (% w/w)	15.0	15.0	15.0
Theoretical quantity of coating applied (% w/w)	10.0	10.0	10.0
Spray rate (g/min)	25–28	210–306	500–650
Coating process efficiency (%)	99.3	99.6	99.6

[a]Machine did not have a device monitoring airflow; fluidizing air was adjusted to maintain a fluidization pattern equivalent to those used on other scales.
[b]Surelease E-7–19010.

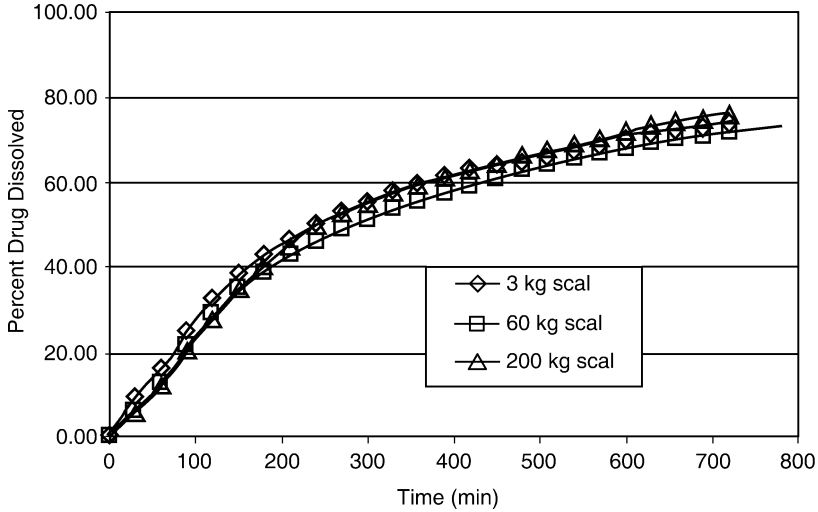

Figure 17 Drug release characteristics of pellets coated on various scales of the Wurster process when the laboratory-scale process, used as the basis for scale-up, has been fully optimized.

up from the 3 kg laboratory scale to a 70 kg pilot scale, and ultimately to a 200 kg production scale. The details of the coating process conditions that were designed for each of these processes are shown in Table 16.

As is readily evident from the information provided in Table 16, the objectives set for coating process efficiencies were easily met. Data representing drug-release characteristics are illustrated in Figure 17, with the clear indication that the equivalent coating process profiles were obtained for each scale of process. With respect to ensuring good coalescence of the latex coating, the f_2 fit factor values were 73.3, 70.6, and 75.4 (for the drug-release characteristics obtained before and after implementation of an oven-curing step) for the laboratory, pilot, and production coating processes, respectively, confirming that the objectives set in this area were also attained.

Hence, once again, the value of taking a systematic, sound scientific approach (and one that excludes personal bias) to process development as the basis for scale-up strategies has been confirmed.

ALTERNATIVE CONSIDERATIONS TO SCALING-UP COATING PROCESSES

Up to this point, the issue of process scale-up has been dealt with in terms of technology transfer from a small- to intermediate- to full production-scale processes. In each case, the coating process is a batch process that gets progressively larger.

During the last decade of the twentieth century, new processing concepts have been introduced that potentially facilitate a paradigm shift as far as pharmaceutical coating process technologies are concerned, and also in terms of how the issue of scale-up may be dealt with.

One approach, fundamentally based on existing processing concepts, involves the adoption of continuous processing technologies. Another introduces a totally different approach to the application of film coatings, and, in doing so, totally changes, and essentially eliminates, most issues as they relate to preparing larger and larger batches of coated products.

Continuous Coating Processes Based on Existing Film-Coating Technologies

The concept of continuous processing, in terms of oral solid dosage forms, is not new to the pharmaceutical industry. Indeed, the tabletting process is a continuous one. Some companies will also lay claim to having introduced continuous coating processes decades ago, but, in each case, these processes have been fundamentally batch/continuous processes where material handling times (involved with unloading and loading the coating vessel between batches) has simply been reduced to a minimum.

The present concept of continuous coating is one in which uncoated product is constantly fed in at one end, and completely coated product comes out at the other end. Processes of this type had their origins in other industries (especially food and agricultural, where batch sizes are routinely much larger than those dealt with in the pharmaceutical industry).

Mancoff (15) and Pentecost (16) have both described continuous film-coating processes that have been primarily designed for pharmaceutical applications. The fundamental basis of such processes is as shown in the schematic outline described in Figure 18.

The inherent advantages exhibited by these processes are that:

- dwell time in the coating vessel is short (approximately 5–15 minutes)
- throughput, on a continuous basis, is typically 500–2000 kg/hr
- the bed depth is much shallower than typically seen in a more conventional pan
- coating uniformity is significantly improved, and, typically, when applying a colored coating, a 2.0% weight gain in the continuous pan provides equivalent coverage to that which can be achieved with a 3.0–4.0% weight gain in a more conventional batch process
- stress on the product being coated is substantially reduced as a result of the shorter residence times (in the process) and the shallower bed depths used

To date, use of such continuous processes has been primarily restricted to the manufacture of large volume products, an application for which

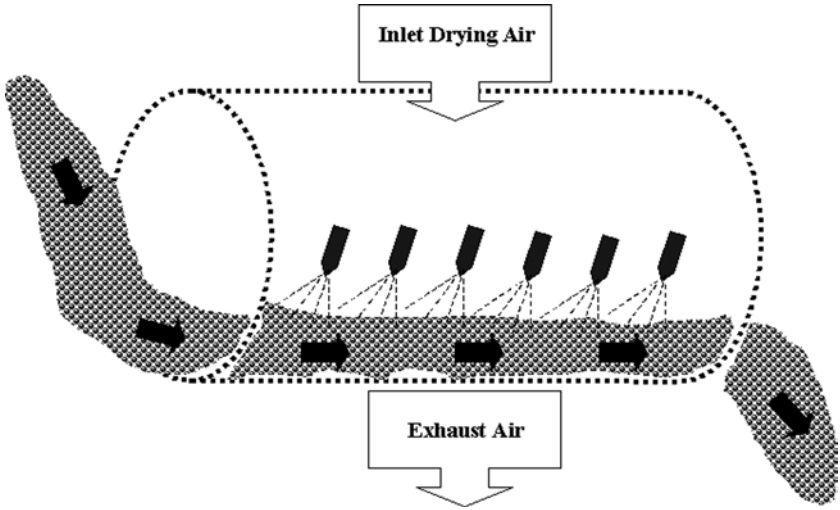

Figure 18 Schematic diagram of a continuous pan-coating process.

continuous processes potentially have a major advantage. Nonetheless, continuous coating processes provide a potentially viable alternative for the scale-up of any film-coating process, where many of the tasks potentially become much simpler, since they would always be the same irrespective of whether the production batch size is 250 kg or 5000 kg. Simplification arises from reducing or eliminating tasks that would otherwise involve:

- deciding appropriate pan loadings
- defining the appropriate number of spray guns to be used
- determining spray application rates
- determining airflow volumes
- defining appropriate gun-to-bed distances

Continuous processes, as they currently exist, do have their limitations, which include the fact that:

- material produced during start-up and shutdown of the process may either have to be scrapped or reworked, since it is likely to have received less than the targeted levels of coating as a result of reduced exposure to the spray-application process
- laboratory-scale continuous processes are essentially non-existent, thus making process development on the laboratory scale more challenging, since processes have to be developed on the basis of a small batch process and then transferred to a continuous process
- the quantity of coating that can be applied in one pass is limited to about a 2.0% weight gain, thus providing a challenge when

applying modified-release coatings where weight gains in the order of 2–10% may be required (unless the use of multiple passes is acceptable). This disadvantage can be offset to some extent when the sprayable solids content of the coating liquid can be increased beyond typical levels of 10–15% w/w. For example, spraying a latex coating at 30% w/w solids would facilitate an increase in the amount of coating deposited to about 4–5%.

It is likely, however, that future developments in this area will allow the advantages of this type of process to be fully realized while addressing and eliminating current disadvantages.

In order to assess what the potential advantages of the continuous process might be, as an alternative to more traditional ones in the scale-up process, it is necessary to determine what the potential throughput rates might be for the continuous process. There are two elements to making such a determination, one based on the thermodynamic limitations of the process, the other on geometric limitations. Throughput (T_{Th}) (kg/hr), based on thermodynamic limitations is essentially given by:

$$T_{Th} = \frac{(SR) \times (SC)}{W} \times 0.06 \tag{3}$$

where SR is spray rate (g/min), SC is the solids content of the coating system (expressed as a decimal fraction, where, e.g., 10% becomes 0.10), and W is the weight gain to be achieved (again expressed as a decimal fraction).

Throughput (T_{geom}) (kg/hr), based on geometric limitations, is given by:

$$T_{geom} = \frac{(A) \times (L) \times (\rho)}{r} \times 0.06 \tag{4}$$

where A is the cross-sectional area of the tablet bed (cm^2), L is the length of the pan (cm), ρ is the bulk density of the tablets (g/cm^3), and r is the tablet residence time in the process (min).

There is a link between the two calculations in terms of residence time, r, which is influenced by thermodynamic issues.

Continuous Processes Based on Electrostatic Powder Deposition

Discussion up to this point has focused on processes involving:

- spraying of liquid coating systems
- "solidifying" the coating through a solvent removal (drying) process,
- coating tablets en masse
- using constant tablet motion, together with other appropriate mixing devices, to facilitate uniform distribution of the coating

These fundamentals provide the basis for many of the difficulties that are encountered as the process is scaled-up.

A more recently introduced concept, described by Staniforth et al. (17), involves the use of electrophotographic principles (essentially those used in the photocopying process) as a basis for the application of dry powder coatings to pharmaceutical tablets. This concept is illustrated in Figure 19.

The salient features of this process are:

- it is continuous
- tablets are handled and coated individually, irrespective of whether the batch size is one tablet or, indeed, one million tablets
- tablets are coated first on one side, and then on the other, thus allowing different coatings (in terms of color, functionality, or both) to be deposited on each side
- the coating zone is defined by the needs of an individual tablet, and the quantity of coating applied is controlled by the magnitude of the electrical field that is created and the electrostatic properties of the powder that is to be deposited
- deposition of the coating is much more precise than is typically achieved using current spray application processes, leading to substantial improvements in coating uniformity both from tablet-to-tablet and across the surface of each individual tablet
- heat fusion takes the place of solvent removal as the means of creating a dry, contiguous coating
- absence of both a drying step and direct tablet-to-tablet contact essentially eliminates those stress factors that are an ever-present feature of the scale-up of more traditional coating processes

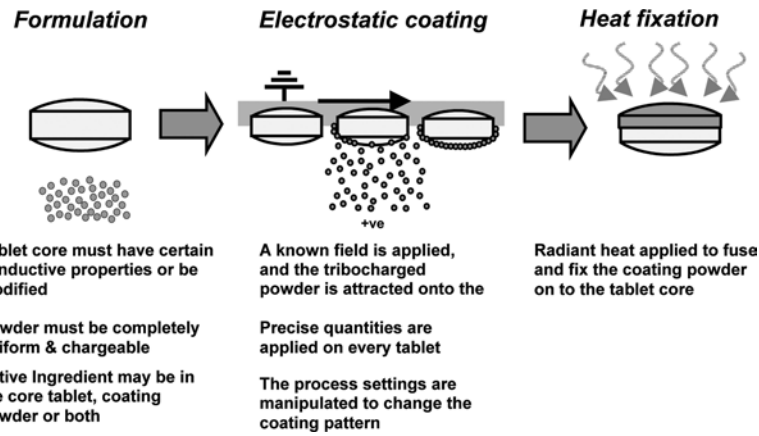
Formulation
Electrostatic coating
Heat fixation
+ve
Tablet core must have certain conductive properties or be modified
Powder must be completely uniform & chargeable
Active Ingredient may be in the core tablet, coating powder or both
A known field is applied, and the tribocharged powder is attracted onto the
Precise quantities are applied on every tablet
The process settings are manipulated to change the coating pattern
Radiant heat applied to fuse and fix the coating powder on to the tablet core

Figure 19 Schematic diagram of a continuous electrostatic powder coating process.

Considering the processing fundamentals of this dry process, almost all of the issues associated with the scale-up of more traditional film-coating processes are eliminated, and the key objective is to feed tablets directly from the tablet press into the electrostatic coating operation, and thence in to packaging. Thus, once the process is defined in terms of coating one tablet, it is replicated an appropriate number of times in order to coat all of the tablets in the batch.

SCALE-UP OF COATING PROCESSES: OVERALL SUMMARY

The characteristics of pharmaceutical coating processes set them apart form most, if not all, other pharmaceutical unit operations, not only in terms of issues that need to be understood during process development, but also when it comes to scaling-up those processes. This is especially true when dealing with the number of process variables that have to be considered. If coating processes are subdivided into pan and fluid-bed processes, then, for those specific types of processes that are routinely employed in the pharmaceutical industry today, it is valid to summarize these processes as belonging to two or three fundamental operating principles. Even if this simplistic view, however, is taken, process scale-up is much more complex than just considering it a case of geometric enlargement.

Spraying of coating liquids, ensuring that effective and consistent drying takes place, achieving appropriate uniformity of distribution of the coating, and enabling final coating structure and functionality to remain consistent with the intended purpose of that coating, are all events that must well defined if successful process scale-up is to be accomplished.

Coming to grips with the multiplicity of parameters that commonly define such a process is clearly facilitated when employing statistical techniques exemplified by the design of experiments approach. Technology transfer on a global scale is equally well facilitated by access to expert systems that capture all of the relevant process and formulation events that have been used to define the final coated dosage form.

Finally, in the long run, the best approach to "trouble shooting" such a complex process is clearly that of "trouble avoidance."

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Innovation and Continuous Improvement in Pharmaceutical Manufacturing

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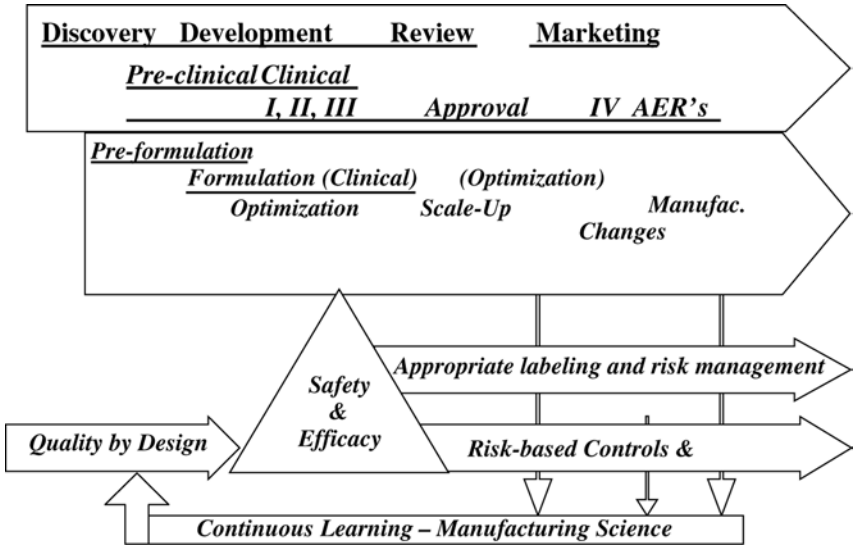
PROLOGUE

Since the publication of the first edition of this, volume much has changed in the world of pharmaceutical quality. The Food and Drug Administration's (FDA) initiatives on Process Analytical Technology (PAT), cGMPs for the 21st Century, and Critical Path have created tremendous opportunities for innovation and continuous improvement in pharmaceutical development and manufacturing (http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm). These opportunities open the door to realize the concept of quality by design and in many ways lead to a realization of a vision represented by the schematic on the cover of the first edition of this book. Within the context of pharmaceutical manufacturing, a combined report of two FDA working groups (the PAT and Manufacturing Science Working Groups) summarizes their learning and challenges with respect to innovation and continuous improvement in the pharmaceutical manufacturing sector. This report is reproduced in this chapter. Based on this report a slightly modified schematic of the vision is proposed below and appears on the cover of this second edition.



THE PAT TEAM AND MANUFACTURING SCIENCE WORKING GROUP REPORT: A SUMMARY OF LEARNING, CONTRIBUTIONS AND PROPOSED NEXT STEPS FOR MOVING TOWARD THE "DESIRED STATE" OF PHARMACEUTICAL MANUFACTURING IN THE 21ST CENTURY

Executive Summary

The health of our citizens depends on the availability of safe, effective and affordable medicines. In the future, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries (e.g., complex drug delivery systems and nanotechnology) and ways of doing business such as individualized therapies or genetically tailored treatments.

Pharmaceutical cGMPs for the 21st Century was intended to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. This report provides an overview of the PAT Team's and Manufacturing Science Working Group's collaborative efforts, accomplishments, and points to consider as the initiative moves into its next phase (implementation and continuous improvement).

The FDA Science Board and the Advisory Committee for Pharmaceutical Science (ACPS) discussions provided information on the current state

of pharmaceutical manufacturing, challenges faced, and opportunities for improvement. These discussions are the primary basis of this report.

Pharmaceutical manufacturing operations are inefficient and costly. The cost of low efficiency is generally not understood or appreciated (e.g., manufacturing costs far exceed those for research and development operations). Low efficiency is predominantly due to "self-imposed" constraints in the system (e.g., static manufacturing processes, focus on testing as opposed to quality by design, approach to specifications based on discrete or the so called "zero tolerance" criteria, a less than optimal understanding of variability, etc.). These constraints keep the system in a corrective action mode.

Continuous improvement is an essential element in a modern quality system and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible. Reducing variability provides a "win-win" opportunity from both public health and industry perspectives, therefore continuous improvement needs to be facilitated.

The PAT Team and the Manufacturing Science Group cooperated internationally to develop a framework to facilitate innovation, application of cutting edge scientific and engineering knowledge, and the principles of modern quality management systems in pharmaceutical manufacturing. A systems approach was adopted to support the initiative's objectives and conform to its guiding principles. The "desired state" for pharmaceutical manufacturing in the 21st Century was articulated and international consensus established. A regulatory framework to support innovation was developed and described in the *PAT Guidance* document. The principles of this framework are being incorporated into the emerging ICH guidance on *Pharmaceutical Development* (ICH Q8).

Quality by design and process understanding principles were used to develop a flexible regulatory system to support innovation in the PAT Guidance. A team approach to CMC review and CGMP inspections, a recognized best practice (e.g., Team Bio), was used to create the PAT Team to provide appropriate risk coverage. Teambuilding and joint training processes were successful in reducing organizational and communication barriers that existed at the beginning of the initiative. Two assignments, a PAT inspection and pre-operational site visit, have been successfully completed by this team.

The pharmaceutical community was asked take on the responsibility for developing standards to support the introduction of innovative tools and technologies under the PAT framework. The ASTM International provided the process to develop these standards using technical expertise in all relevant disciplines from the pharmaceutical community and other industrial sectors. A significant support infrastructure for the desired state is emerging in several academic and scientific organizations and associations.

A second PAT team is planned and will include CDER's Office of Biotechnology, Office of Compliance and ORA Team-Bio representatives. Formation of the second PAT Team will provide an additional opportunity to develop close collaboration and cooperation between the PAT team and Team-Bio. Lessons learned from the PAT Team and Team-Bio should also be utilized to identify best practices and to develop recommendations for a broader team approach.

ICH Q8 will describe the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. It is not intended to be a "how to" guidance. It will provide sponsors of drug applications an opportunity to present knowledge gained during development of a product and its manufacturing process and relevant prior knowledge. It will indicate areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches to support continuous improvement.

The PAT framework and ICH Q8 will provide a basis for risk mitigation. Risk management principles and tools being developed under ICH Q9 will be necessary to describe and communicate the level of risk-mitigation achieved through quality by design and process understanding.

Although to a large degree consensus has been established on the "desired state," it is recognized that there is often a tendency for a consensus on collective ends to attenuate when specifics are addressed. This is often due to divergent understanding of the problem being addressed and/or differences in interests and issues in representation of the problem being addressed.

Under the ACPS Manufacturing Subcommittee a working group will be formed to identify specific steps needed to move towards the desired state. The group will also develop illustrative case studies to support the ICH Q8 document and CPG 7132c.08. ICH Q8 and illustrative examples should then be a basis to develop the draft comparability guidance to facilitate continuous improvements.

The combined work products of the CGMP Initiative are positioned well to provide a comprehensive set of regulatory tools to facilitate a move towards the desired state. Only companies that achieve a high level of process understanding will have the opportunity to use their information to justify a more flexible regulatory path towards continuous improvement. The proposed ICH Q10 should utilize these regulatory polices to provide additional guidance on quality system for change control under CGMPs to facilitate continuous improvement.

Significant challenges lie ahead for the pharmaceutical community and for regulators to move to the "desired state" for pharmaceutical manufacturing in the 21st century. Nevertheless, critically important steps have already been taken.

Introduction

Pharmaceuticals will have an increasingly prominent role in the health care of the future. The health of our citizens depends on the availability of safe, effective and affordable medicines. In the future, pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, and the best principles of quality management to respond to the challenges of new discoveries (e.g., complex drug delivery systems and nanotechnology) and ways of doing business such as individualized therapies or genetically tailored treatments.

Regulation of the future will also need to meet these challenges, by incorporating new scientific information into regulatory standards and policies. Both industry and regulatory practices will need to be informed by the best techniques of risk assessment and management. "Pharmaceutical cGMPs for the 21st Century" is intended to enhance and modernize the regulation of pharmaceutical manufacturing and product quality.

Under the CGMP Initiative the PAT Team and the Manufacturing Science Group cooperated internationally to develop a framework to facilitate innovation, application of cutting edge scientific and engineering knowledge, and the principles of modern quality management systems in pharmaceutical manufacturing. This report provides an overview of these collaborative efforts, accomplishments, and points to consider as the initiative moves into its next phase (implementation and continuous improvement).

Pharmaceutical Manufacturing: Challenges and Opportunities

The FDA Science Board (1) and the Advisory Committee for Pharmaceutical Science (2) discussions on the current state of pharmaceutical manufacturing, challenges faced, and opportunities for improvement are the primary basis of this report. Information gathered at several national and international scientific workshops provided examples of scientific and technological opportunities and afforded the opportunity to debate and develop a shared vision for the future. This vision is articulated as the "desired state" for pharmaceutical manufacturing in the 21st century.

A Regulatory Framework for Manufacturing Science: A Systems Perspective

The PAT Initiative and the PAT Team preceded the CGMP Initiative by about a year; subsequently, the PAT Initiative became a part of the broader CGMP Initiative. Their efforts were directed towards developing a regulatory framework to *encourage the early adoption of new technological advances by the pharmaceutical industry*. The Manufacturing Science Working Group's efforts were directed towards enhancing manufacturing science knowledge available to the agency to ensure that *regulatory review and inspection policies are based on state-of-the-art pharmaceutical science.*

A systems approach was adopted to ensure appropriate linkage and support for all objectives of the CGMP Initiative; i.e., (i) *encourage the early adoption of new technological advances by the pharmaceutical industry*, (ii) *base regulatory review and inspection policies on state-of-the-art pharmaceutical science*, (iii) *facilitate industry application of modern quality management systems*, (iv) *use risk-based approaches that focus both industry and agency attention on critical areas*; and (v) *incorporate enhanced quality system approaches into the agency's business processes.* Inspiration for a systems approach was derived from the body of work by leaders in modern quality management such as Shewhart, Deming, Juran, Box, Taguchi, and others (3–6). This is reflected in the "desired state" and the regulatory framework described in the *PAT Guidance* document. The principles of this framework were presented to the ICH and these are being considered in the emerging guidance on *Pharmaceutical Development* (ICH Q8).

Continuous improvement is an essential element in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. Improvement efforts are carried out in a structured manner with appropriate pre-defined protocol and oversight. These efforts are primarily directed towards reducing variability in process and product quality characteristics and are not for changing the fundamental design of a manufacturing process (5). For continuous improvement products should already be in compliance with their specifications and process improvement steps (e.g., adjustment of process parameters, introduction of new equipment of the same design,and operating principles with advanced control options) should be within the original "design space." That is, such improvement steps are not considered as "changes" because product quality and performance (e.g., bioavailability, shelf-life) are assured.

Generally the term *continuous improvement* is broadly used for all improvement efforts including *corrective actions* and the ensuing *preventive actions*. In the regulatory setting a distinction between corrective action and continuous improvement is essential. Need for corrective actions occur when product quality characteristics are in question (e.g., out of specification). Such a situation can require urgent risk assessment and sound quality decisions to prevent any adverse impact on patients.

Innovation is different from continuous improvement since it is not a part of routine production operations and requires significant investment of resources and may require changes in production design and operation. Therefore, three types of improvement approaches—*innovation*, *continuous improvement*, and *corrective actions*—are distinguished. These approaches and their roles in a quality system are shown in Figure 1. The simple phrases used in Figure 1 to describe a modern quality system were suggested by the FDA's Quality System Working Group. Some distinguishing characteristics of the three improvement approaches and the contributions

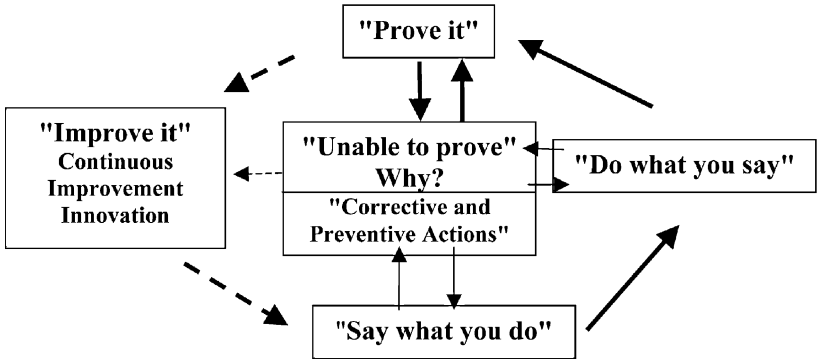


Figure 1 Types of "improvement."

of the two groups are summarized in Table 1. A need for similar distinction between improvement approaches was previously suggested in the automotive industry (7).

Format of This Report

The report is organized into six sections. The following section (section "The Current State and the Desired State of Pharmaceutical Manufacturing in the 21st Century") describes the "current state" and the "desired state." The primary contributions of the two groups are described in section "Accomplishments: Primary objectives", followed by "points to consider" (section "A Systems Perspective: 'Points to Consider'") and recommendations for other groups of the initiative (section "Collaborations and Recommendations"). The final section (section "Next Steps and Considerations for the Critical Path Initiative") proposes next steps and identifies broad areas for research and training under the Critical Path Initiative. Table 2 provides a summary of primary accomplishments of the two groups within the context of the Initiative's five guiding principles and objectives (dark shading). Contributions to, or impact on, other objectives are outlined as "points to consider." Many of these "points to consider" are based on some of the 14 points for a quality management system articulated by Deming (3). In Table 2, current and/or planned collaborations with other groups are based on the lessons learned [ ]; recommendations for other groups in the initiative are identified { }.

The "Current State" and the "Desired State" of Pharmaceutical Manufacturing in the 21st Century

The "Current State"

Pharmaceutical manufacturing operations are inefficient and costly. Compared to other industrial sectors, the rate of introduction of modern

Table 1 Types of Improvement and Their Relation to the Objectives of the FDA Initiatives

	Improvement approaches	Characteristics and objectives
Innovation		
	Primary focus area of the PAT TeamManufacturing Science WG is contributing to harmonization of the PAT framework in ICH	Revolutionary, to be a leader Focused applications—project based Significant capital expenditure, ROI, top-down Strong research component Technical experts involved New findings and improved knowledge *CGMP initiative objective #1*
Continuous improvement	PAT framework provides many options and opportunities including research data collection in production Manufacturing Science WG creating regulatory flexibility through ICH Q8	Product is in specification Acceptance criteria—variable/continuous data Evolutionary, incremental process optimization, continuous, daily activity Carried out by plant and quality staff *CGMP initiative objective #1–5*
Corrective actions	PAT opens the door for new tools for root cause investigations and data collection in production Manufacturing Science provides the foundation for more effective approaches	Product is out of specification (OOS) or procedural deviations "Crisis"—immediate action needed Required by regulators

Abbreviations: FDA, food and drug administration; PAT, process analytical technology.

Table 2 Report of the FDA's CGMP for the 21st Century Initiative's PAT Team and the Manufacturing Science Working Group[a]

	OBJECTIVES				
GUIDING PRINCIPLES	**Encourage new technological advances**	**State-of-the-art pharmaceutical science**	**Risk-based approaches focus industry and agency attention on critical areas**	**Facilitate industry application of modern quality management**	**Enhanced quality systems approaches into the agency's business processes**
Strong public health protection	Improve focus on process understanding and control	Improve focus on "quality by design" and clinical relevance	Reduce uncertainty to enable risk-based decisions	"Out of the corrective action crisis" to continuous improvement	Team approach to CMC review and CGMP inspections
Science-based policies and standards	PAT guidance; ASTM standards	ICH Q8; [CPG 7132c.08] [ICH Q9] [{Comparability Protocol}] {Proposed ICH Q10}	Critical variables—clinical relevance	Science-based regulatory flexibility for continuous improvement	Scientific foundation of the FDAs quality system
Risk-based orientation	Regulatory scrutiny based on the level of scientific understanding	Mechanistic basis for understanding failure modes and variability	Sources of variability and "risk to quality"	"Drive out fear"	Continuous improvement—Change control and life cycle management

(*Continued*)

Table 2 Report of the FDA's CGMP for the 21st Century Initiative's PAT Team and the Manufacturing Science Working Group[a] (*Continued*)

	OBJECTIVES				
GUIDING PRINCIPLES	**Encourage new technological advances**	**State-of-the-art pharmaceutical science**	**Risk-based approaches focus industry and agency attention on critical areas**	**Facilitate industry application of modern quality management**	**Enhanced quality systems approaches into the agency's business processes**
Integrated quality systems orientation	PAT team: training, certification, and continuous learning [Team Bio]	Strengthen our education and research infrastructure [{Product Specialist—Pharmaceutical Inspectorate}]	Risk communication: Knowledge transfer [Risk-based site selection for CGMP Inspections]	"Pride of workmanship" and continuous learning	"Pride of workmanship" and continuous learning
International cooperation	Communication, workshop, plans for joint training	ICH process, shared vision and "desired state"	Emerging infrastructure for the "desired state"	"Breakdown organizational barriers"	Continuous improvement—Change control and life cycle management

[a]Current and/or planned collaborations with other groups, based on lessons learned are shown in [ ]; recommendations for other groups in the initiative are identified in { }. *Abbreviations*: PAT, process analytical technology; FDA, food and drug administration.

engineering process design principles, new measurement and control technologies, and knowledge management systems is low. Opportunities for improving efficiency and quality assurance through an improved focus on design and control, from an engineering perspective, are not generally well recognized. For example, when discussions at the FDA Science Board and Advisory Committee for Pharmaceutical Science shed light on the current low efficiency and its cost implications (e.g., costs associated with manufacturing can far exceed those for research and development operations in innovator pharmaceutical firms) many at FDA had difficulty understanding this and common reactions were "how could this be possible?" or "this can't be true."

Discussion of the current state by major publications such as The Economist (8), the Wall Street Journal (9) and the Business Week (10) add to a growing awareness of a need for improvement. An excellent analysis of the current state of manufacturing process innovation in pharmaceutical and biotechnology industry was described in 1996 by Pisano (11).

Over the last decade a mind-set has evolved among many pharmaceutical business leaders and others that manufacturing is no longer a necessary "strategic competency." This view probably contributes to the general lack of private and public support for fundamental science and process innovation and to the perception that manufacturing is a "step-child" in this industry. Efficient manufacturing process can reduce manufacturing costs, and this itself can be a significant competitive advantage. Effective and efficient process development contributes more towards a company's ability to accelerate time to market, ramp up production rapidly, enhance customer acceptance of new products, and develop a stronger proprietary position (11).

The public health objectives and the competitive power of new product development are well recognized. Development of new more efficient and effective manufacturing process technology often fails to generate any excitement among academics, practitioners and the public at large; since these groups often only come in contact with innovative products and not with the manufacturing process that delivers these products. A recent estimate of potential world-wide cost-savings from efficiency improvement is suggested to be as high as US $90 billon (12). This would be equivalent to the current cost of developing 80–90 new drugs every year. A rigorous economic analysis to obtain robust estimates of cost savings may help to put an end to the lingering question—"how could this be possible?"—and to fully engage the pharmaceutical community for developing approaches to realize the potential "win-win" opportunities.

Quality and productivity improvement share a common element-reduction in variability through process understanding. Reducing variability provides a "win-win" opportunity from both public health and industry perspectives. And, since pharmaceutical product manufacturing technologies and practices are generally similar between both innovator and generic

companies, facilitating efficiency improvements provide opportunities for both sectors of the pharmaceutical industry. An efficient and secure U.S. pharmaceutical manufacturing sector will be essential in the 21st Century.

Low Efficiency: Contributing Factors

Often it is suggested that regulatory policies and practices contribute to the current low efficiency. Regulators and many in manufacturing operations express their frustration by suggesting that manufacturing is a "step-child" in this industry, and that there is no economic motivation (e.g., cost and price difference) for improvement. Other suggestions include a general lack of systems perspective, organizational barriers that inhibit exchange of knowledge, and the attitude that much of pharmaceutical formulation and process development is an "art." Some in pharmaceutical development suggest that there are very limited opportunities ("development time crunch") to realize and/or demonstrate the level of science underlying current formulation and process development efforts (13). Clearly these are complex and interrelated issues. Only regulatory and scientific challenges are discussed in the following sections.

Discussions at FDA Science Board and Advisory Committee meetings, scientific workshops and conferences identified the following major contributing factors:

- Routine pharmaceutical production is conducted by running a plant at rigidly defined operating conditions described in Standard Operating Procedures (SOP's). A regulatory submission may contain limited information (e.g., manufacturing process and parameters used for *bio-batch* manufacturing and its *executed batch record*) and these conditions then become regulatory commitments. Plant operators are then expected to always reproduce exactly these same set of conditions. During routine production adherence to conditions in SOP's and laboratory evaluation of in-process and final product characteristics provide assurance that products produced will have the safety and efficacy profile outlined in the approved product label. This type of operation may be considered a "static manufacturing operation." Because it is based on limited data, any change generally requires regulatory notification and in many cases prior approval.
- Static manufacturing can create, or is a result of, a mind-set that "the product is approved and validated—do not change."
- Process control is predominantly based on documented evidence of conformance to SOP's, which generally include a "fixed process time" and laboratory based testing of in-process materials.
    - This approach requires a high level of control on incoming raw material characteristics.

  - Physical characteristics of pharmaceutical materials (e.g., excipients), as related to their functionality in *process*, are not well understood.

- Deviations from established standard operating procedures and out of specification (OOS) observations can occur frequently.
  - OOS investigations that follow take significant (time) resources and have a low rate of success in finding permanent corrective and preventive solutions.
  - Often batches have to be rejected (internal failure) due to an inability to document quality assurance.
- Variability and/or uncertainty in a measurement system for physical characteristics such as particle size and dissolution can pose significant challenges when OOS results are observed.
- Acceptable quality characteristics, or specifications, are generally described in terms of discrete or attribute data (e.g., pass/fail; or no unit outside 75% to 125%) and are inappropriately referred to as "zero defect or tolerance" (since these are for the sample tested).
  - The OOS rate can increase with increasing test sample size; investigations to identify sources of variability (beyond available information in batch records) and robust estimates of variability are difficult and discouraged (since increasing sample size increases the risk of OOS).
  - It is difficult to differentiate inherent or natural variability (or common cause variability) from variability due to special causes.
- Information needed for process improvement can be in a different organization and often not available at the right time.

Continuous Improvement Needs Higher Level of Process Understanding

When OOS results are observed there are few, if any, means to re-examine the fundamental design aspects of a product/process and/or to evaluate the (clinical) relevance of established specification (quality by design). In production, the focus is predominantly limited to "quality of conformance." In terms of risk to conformance; *quality is inversely proportional to variability and quality improvement efforts are directed towards reducing variability* (14). Determining corrective and preventive actions without a sound understanding of sources of variability, and robust estimates of variability, are difficult. And, in the absence of good information, attempts to adjust a process can potentially create new problems. Since continuous improvement can only occur when a product is already in compliance, considering the challenges identified above (e.g., "zero tolerance," variability and/or uncertainty in

measurement systems, etc.), continuous improvement is difficult (if not impossible) in the current state.

- Lack of information and knowledge creates an uncertain environment that precludes risk-based decisions.
  - Static manufacturing processes and reliance on laboratory testing as a means for control are, in part, a result of insufficient information available during the CMC review process. In the absence of an adequate level of process understanding, specifications have to be established without adequate knowledge of variability in the clinical trial products and its clinical relevance.
- Measurement system variability can be a significant part of total variability.
  - Estimates of process variability are based on measurement of variability in quality characteristics of in-process materials and products. The measurement system (sampling, sample preparation, analytical method, operator training, etc.) then is the "*lens through which we observe a process*" and its variability can contribute to OOS observations and can be the limit to which we can observe and/or improve a manufacturing process.
  - Over the last three decades tremendous progress has been made in analytical chemistry and variability in chemical methods has been reduced dramatically. The situation is quite different for methods used to measure physical characteristics.
  - Currently significant challenges exist for managing variability in sampling and sample preparation (e.g., for blend uniformity and particle size testing), and analytical instruments for physical characteristics such as dissolution and particle size.
    - Current tests are generally destructive (i.e., sample is altered or destroyed) and robust estimates of measurement system variability (all aspects of the procedure including the operators) are difficult to obtain without using methods such as Gauge R&R-reproducibility and repeatability (14). Suitability of current methods then is based on calibration using a calibrator system that has its own built-in variability and other assumptions (e.g., in physical testing such characteristics as size, shape, density can alter aerodynamic and/or hydrodynamic behavior of materials in a test system and contribute to systems variability).
  - In the absence of robust estimates of measurement system variability and with the inability to verify the inherent assumptions in a measurement system, attempts at improving a manufacturing process can be difficult and, if attempted, can potentially

create new problems (e.g., in case of common cause variability, process adjustments can make a system unstable) (3).

- The term "in-process testing" is synonymous with "process control." From an engineering perspective tests at the end of a process do not provide any direct means to keep a process under "control." It is well recognized that such tests "*simply accept or reject lots*" and depending on the operating characteristic curve of a test "*accepted lots are no better than the rejected ones*" (14).
    - A multidisciplinary communication challenge and a general lack of awareness of scientific developments in different disciplines contribute to a suspicion about the level of control achieved through product and process design (the "art" argument). The pharmaceutical science and engineering knowledge developed over the last two decades is not optimally relied upon for decision making in regulatory and/or quality assurance settings.
    - The value and utility of new advances in process technologies such as on-line process analyzers and controls (e.g., feedforward and feedback controls) are not widely recognized. A common misperception is that testing is the only valid approach; when in fact, reliance on testing for quality assurance is a 19th Century concept and is a lesser form of quality assurance compared to what can be achieved through design and control. The CGMP regulations and practices have long recognized this principle. The following quote from an FDA Warning Letter illustrates this principle: "*The practice of partial releases, no matter how stringent the re-sampling, raises doubt as to the safety and efficacy of the product being released. It is not acceptable to substitute testing over adequate control of a process*."
- Similar and repeating OOS observations (e.g., dissolution failures) for different products across the industry and the inability to find "root causes" suggest that some of these observations may be due to variability from "common causes" (i.e., inherent variability in raw materials, equipment, measurement system etc.).
    - Furthermore, variable and unstable external calibrators (e.g., USP Prednisone Tablets RS) raise questions with regard to the stability of a measurement system. Organizational and functional barriers (e.g., analytical and production) add to this challenge through an information/knowledge gap or disconnect between measurement and manufacturing process and questions on stability, reproducibility, and repeatability of the measurement system in the context of variability and OOS may not be addressed adequately.

- When the source of variability is from common cause(s) it is essentially a part of the clinical trial materials and, therefore, included in the clinical assessment of safety and efficacy and part of the FDA approval decision.
    - Adequate characterization of clinical trial materials to describe variability in quality characteristics and the application of "robust design" principles (6) can provide opportunities for reducing (regulatory) uncertainties regarding product failure modes, reliability of controls to prevent failures and the level of quality assurance achieved by design.
    - Reducing uncertainty is a prerequisite for sound risk-based decisions.

"The Desired State" of Pharmaceutical Manufacturing in the 21st Century

Improving the foundation of manufacturing science in our current manufacturing practices should be the primary basis for moving away from the corrective action "crisis" to continuous improvement. Knowledge of the "variation theory" is, therefore, an essential element of manufacturing science. It requires an in-depth understanding of a process or system (15):

> "*Cease dependence on inspection* [testing]. *Depending on inspection is like treating a symptom while the disease is killing you. The need for inspection results from excessive variability in the process. The disease is variability. Ceasing dependence on inspection means you must understand your processes so well that you can predict the quality of their outputs from upstream activities and measurements. To accomplish this you must have a thorough understanding of the sources of variation in your processes and then work towards reducing the variation. Ceasing dependence on inspection forces you to reduce variability.*"

The "desired state" for pharmaceutical manufacturing in the 21st Century therefore emphasizes and aims to improve knowledge on design and understanding of product and processes. When such information and knowledge is shared with FDA it can then be a basis to recognize different levels of understanding achieved by companies and to utilize this information in risk-based decision criteria. With this as the background, the "desired state" was articulated in the second progress report of the CGMP Initiative (February 20th 2003):

> *Pharmaceutical manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions in establishing specifications and evaluating manufacturing processes can substantially improve the*

efficiency of both manufacturing and regulatory processes. This initiative is designed to do just that through an integrated systems approach to product quality regulation founded on sound science and engineering principles for assessing and mitigating risks of poor product and process quality in the context of the intended use of pharmaceutical products. In this regard, the desired future state of pharmaceutical manufacturing may be characterized as:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes.
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.
- Continuous "real time" assurance of quality.
- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability.
- Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.

This description reflects a view from the manufacturing side—"beginning with the end in mind." Therefore, the goal "*Product quality and performance achieved and assured by design of effective and efficient manufacturing processes*" is placed before "*Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.*"

Mechanistic understanding, as opposed to data derived from one-factor-at-time type of experiment or simple correlative information, provides a higher level of knowledge and an ability to generalize within certain constraints. This provides an opportunity to develop a flexible regulatory system with appropriate risk coverage; for example a team approach to CMC reviews and CGMP inspections (e.g., need for prior approval of post approval changes vs. information to be held on site and available during inspections).

A manufacturing process is generally considered well understood when (i) all critical sources of variability are identified and explained, (ii) variability is managed by the process, and (iii) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions. The ability to predict reflects a high degree of process understanding. Companies that achieve a high level of process understanding should have an opportunity to use their information to justify a more flexible regulatory path towards continuous improvement.

Risk-based decision criteria would then have to relate to clinical relevance; different levels of understanding (e.g., correlative, causal, mechanistic) will need to be recognized within this context. This general approach is utilized in some current regulatory policies; in the desired state the approach can be extended to other areas. For example in current regulatory policies;

- Establishing in vitro in vivo correlation (IVIVC) for modified release dosage form provides a justification for waiving *in vivo* bioequivalence evaluation only for certain specified post approval changes. Since a correlation is dependent on the mechanism of drug release, it is not used in situations that could potentially alter its mechanism (16).
- Waiver of *in vivo* bioequivalence studies for major post approval manufacturing changes for the BCS Class I (Biopharmaceutics Classification System; highly soluble, highly permeable and rapidly dissolving) solid oral products is NOT recommended for narrow therapeutic index drugs (17).

An objective metric is needed to gauge the level of manufacturing process understandings and control achieved—*process capability* can be this metric. During development studies, process capability analysis can be performed in terms of probability distribution (type of distribution, mean and variability) without regard to specifications (14); such analysis can provide useful supporting information on variability and may provide additional support for proposed regulatory acceptance criteria. Inherent variability in clinical materials can then be a benchmark and a basis for continuous improvement.

The quality of design (product and its manufacturing process)—the ability to reliably predict quality and performance, process monitoring and controls, process capability and appropriate risk-mitigation strategies—provides an opportunity to achieve ''real time'' quality assurance (the ultimate level of efficiency). This also provides an excellent opportunity to develop efficient and effective quality assurance systems as an alternative to market or public standards (18).

Assessment of process capability and statistical process control brings the ability to distinguish between a stable and un-stable process and provides a means to distinguish between different causes of variability, e.g., common cause, special cause, structural (e.g., seasonal), and tampering (e.g., deliberate or unintentional). Process understanding, quality by design and capability analysis can facilitate risk-based regulatory decisions for continuous improvements:

- *Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability*.

- *Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.*

It is expected that different companies will develop different levels of process understanding and the level of understanding for a particular product can increase over time (life cycle). These differences will need to be accommodated in regulatory policies through a clear articulation of what is a minimum regulatory expectation (e.g., current requirements of CMC review information and process validation) and what is an optional opportunity for companies to improve efficiency while reducing risk to quality and regulatory concerns.

Accomplishments: Primary Objectives

Encourage New Technological Advances

Strong Public Health Protection: The basic tenant of a modern quality system is that quality *cannot be tested into products; it should be built in by design*. An emphasis on *building quality into products* allows an improved focus on relevant multi-factorial relationships among material factors, manufacturing process and environmental variables, and their collective impact on quality. These relationships provide a basis for identifying and understanding interactions among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls, SOP's, training). This can improve identification and evaluation of product and process variables that are critical to product quality and performance. A higher level of process understanding should reduce uncertainty and improve FDA's ability to make scientific risk-based decisions.

The PAT guidance facilitates introduction of new measurement and control tools in conjunction with well-established statistical methods such as design of experiments and statistical process control. It, therefore, can provide more effective means for product and process design and control, alternate efficient approaches for quality assurance, and a means for moving away from the corrective action to a continuous improvement paradigm.

Science-Based Policies and Standards

Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (19): This guidance describes a regulatory framework that will encourage the voluntary development and implementation of innovative approaches in pharmaceutical development, manufacturing, and quality assurance. Many new

technologies are currently available that provide information on physical, chemical, (micro)biological characteristics of materials to improve process understanding and to measure, control, and/or predict quality and performance. The guidance facilitates introduction of such new technologies to improve efficiency and effectiveness of manufacturing process design and control (e.g., feedforward and feedback controls) and quality assurance. Gains in quality and efficiency will vary depending on a process and a product, and are likely to come from:

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls.
- Preventing rejects, scrap, and re-processing.
- Real time release.
- Increasing automation to improve operator safety and reduce human error.
- Improving energy and material use and increasing capacity.
- Facilitating continuous processing to improve efficiency and manage variability.

ASTM International Technical Committee E55: Pharmaceutical Applications of Process Analytical Technology (20): Innovation in manufacturing is the responsibility of private sector and non-regulatory public sector. The PAT Guidance provided the regulatory framework to facilitate innovation in the interest of the public health. FDA resources are limited and have to be focused on core regulatory responsibilities. Therefore, the broader pharmaceutical community should take on the responsibility for developing standards to support the introduction of innovative tools and technologies. In this regard, ASTM International provides an excellent process to develop standards in a timely manner using technical expertise in all relevant disciplines from the pharmaceutical community and other industrial sectors. Therefore, the FDA's PAT team worked with ASTM to establish Technical Committee E55 on Pharmaceutical Application of Process Analytical Technology.

Focusing on process monitoring and control, instead of testing, requires process control standards consistent with guiding principles of the control theory. ASTM provides an opportunity to bring a strong engineering process control perspective and to learn from other industrial sectors that have utilized process analyzers and controls for many years. The E55 committee is tasked with developing standards related to process analytical technology with the primary focus on process understanding and control. The PAT Team is represented on E55 committees. Three subcommittees of E55 include: PAT System Management, PAT System Implementation and Practice, and PAT Terminology. The standard *E2363-04: Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry* was recently published.

Risk-Based Orientation: The PAT Guidance recognizes that within an established quality system and for a particular manufacturing process, one would expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product. For processes that are well understood, opportunities exist to develop less restrictive regulatory approaches to manage change.

Collaboration with the Risk-Based Site Selection Working Group of the initiative is on-going. Development of ICH Q9 guidance will provide additional risk tools and principles and facilitate international harmonization of these principles.

Integrated Quality System Orientation: By definition PAT brings a systems perspective on design and control of manufacturing processes. Therefore, a systems approach is needed for regulatory assessment of PAT applications. To achieve this objective, the PAT Team for CMC review and CGMP inspection was created. It includes reviewers, investigators and compliance officers. A comprehensive scientific training program was developed with guidance from the Advisory Committee for Pharmaceutical Science's PAT Subcommittee. The training (didactic and practicum) was provided by academic and industrial experts. Three scientific disciplines, process analytical chemistry (University of Washington, Seattle; National Science Foundation (NSF) Center for Process Analytical Chemistry); industrial and physical pharmacy (Purdue University; NSF Center for Pharmaceutical Process Research), and chemical engineering (University of Tennessee; NSF Measurement Control Engineering Center) were included in training for the PAT Team.

The team members trained together. As a part of their certification process they were asked to work as a team to address comments received on the draft guidance. Two assignments, a PAT inspection and pre-operational site visit, have been successfully completed by this team. Several team members have participated in a number of scientific conferences. The feedback received from their instructors, conference participants and companies has been very positive. The many organizational and communication barriers that existed at the beginning of the initiative are being removed and the team members are functioning as a team committed to a common purpose.

The integrated quality system orientation afforded a flexible regulatory approach for implementation of PAT. For example, regulatory implementation plans can include:

- PAT can be implemented under the facility's own quality system. CGMP inspections by the PAT Team or PAT certified investigator can precede, or follow, PAT implementation.
- A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection

can be performed by a PAT Team or PAT-Certified Investigator before implementation.

- A *comparability protocol* can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. Following approval of this *comparability protocol* by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation.

International Cooperation: Extensive international scientific collaboration was sought from the very beginning. For example, before the July 2001 ACPS discussion on PAT, FDA staff participated in the Royal Pharmaceutical Society's New Technology Forum (a collaborative effort between the Medicines Control Agency, now referred to as the Medicines and Healthcare Products Regulatory Agency, and the British pharmaceutical industry). These discussions were very valuable and contributed in the development of the FDA's PAT Initiative (21). The list of international scientific conferences and workshops on PAT in the past three years is too long to list. Almost every pharmaceutical scientific association in the United States, Europe, and Japan has organized PAT conferences, and some have made PAT conferences an annual event (for example, the International Society of Pharmaceutical Engineering (ISPE) and the International Forum of Process Analytical Chemistry (IFPAC)). The Pharmaceutical Technology section of the American Association of Pharmaceutical Sciences in collaboration with the Royal Pharmaceutical Society organized two consecutive Arden House Conferences in the US and UK on the FDA Initiatives in 2003 (PAT Initiative) and the proposed "desired state" of pharmaceutical manufacturing (2004). These and other scientific conferences afforded an opportunity to discuss the FDA initiative with industry, academia and regulatory colleagues from Canada, Europe and Japan.

The European Medicines Agency has established an EMEA PAT team and established contact with FDA's PAT team. In the near future FDA plans to share with the EMEA Team PAT training materials and lessons learned.

Following the issuance of the PAT Guidance workshops are planned in the three ICH regions. The European Workshop will provide an opportunity for the EMEA and FDA PAT teams to further collaborate on regulatory implementation of PAT. Similarly the planned workshop in Japan will afford an opportunity to further strengthen the collaboration between FDA and MHLW. Health Canada has been invited to participate with FDA in the second PAT training program planned for the 2004–2005 fiscal year.

The definition of PAT in the FDA guidance and ASTM E55 and other concepts are being incorporated into the ICH Q8 guidance. The ASTM

International provides another venue for international cooperation and the current E55 membership reflects broad international interest in these standards.

Several academic institutions in the US, Europe, Switzerland, and Japan have incorporated PAT concepts in their curricula. Some of the FDA PAT Team members have been requested to serve as adjunct professors to teach and to participate on doctoral dissertation committees on PAT research projects.

State-of-the-Art Pharmaceutical Science

Strong Public Health Protection: Information on pharmaceutical development studies in new drug applications is generally limited and varies from application to application. This creates an uncertain environment and curtails FDA reviewers' ability to make risk-based decisions and inhibits their ability to recognize and assess how quality was built in. Risk communication between review and inspection staff is also inhibited. Appropriate pharmaceutical development information can improve public health by improving FDA's risk-based decisions and by facilitating continuous improvement.

Science-Based Policies and Standards: During the July 2003 ICH meeting in Brussels, agreement was reached on a common vision and approach for developing an international plan for a harmonized pharmaceutical quality system that would be applicable across the life cycle of a product. This plan emphasizes an integrated approach to review (assessment) and inspection based on scientific risk assessment and risk management. Several actions were outlined to implement this vision. An expert-working group (ICH Q8 EWG) was established to develop guidance for pharmaceutical development.

The ''desired state'' description was adopted with slight modification:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes.
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.
- An ability to affect continuous improvement and continuous ''real time'' assurance of quality.

The ICH Q8 guidance is currently being developed and is expected to reach the ICH Step 2 in November 2004. It is intended to provide guidance on the contents of Section State-of-the-the-Art Pharmaceutical Science. P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH topic M4).

Risk-Based Orientation: Collaboration with the ICH Q9 is an important element. This collaboration will provide a means to connect the scientific

framework in ICH Q8 to risk-management principles being developed by ICH Q9.

ICH Q8 creates an opportunity for an applicant to demonstrate an enhanced knowledge of product performance over a wider range of material attributes (e.g. particle size distribution, moisture content, and flow properties), processing options and process parameters. This knowledge can be gained in a structured manner by, for example, applications of formal experimental designs, PAT concepts, or risk management tools (e.g., failure mode effect analysis or FMEA). Such knowledge can allow regulatory agencies to develop more flexible regulatory approaches, for example, to:

- facilitate risk based regulatory decisions (reviews and inspections);
- implement manufacturing process improvements, within the boundaries of the knowledge described in the dossier, without the need for regulatory review;
- implement "real time" quality control, leading to a reduction of end-product release testing

Integrated Quality System Orientation: The ICH Q8 guidance on Pharmaceutical Development section is intended for use both by CMC reviewers and CGMP investigators. Because the aim of pharmaceutical development is to design a quality product and a manufacturing process to deliver the product in a reproducible manner, the information and knowledge gained from pharmaceutical development studies should provide additional scientific understanding to support establishing more relevant specifications and manufacturing controls.

Information from pharmaceutical development studies can be the basis for risk management when these studies are designed with the aim of demonstrating that quality was *built in by design*. This document and the manufacturing science framework provide an area of "common interest" and opportunity for collaboration between the CMC review and CGMP investigations staff.

International Cooperation: The Manufacturing Science Working Group collaborated with the Product Quality Research Institute (PQRI) to organize the first workshop (April, 2003) of the CGMP Initiative. This was an international workshop and provided an opportunity to explain the goals and objectives of the initiative and to seek stakeholder input (http://www.pqri.org/gmpworkshop/).

A second workshop was organized in The Netherlands (November 19–21, 2003) by the International Pharmaceutical Federation (FIP). This was in collaboration with FDA, EMEA, and other European trade and professional associations (EFPIA, EUFEPS, APIC/CEFIC and IPEC) http://www.qualityworkshop.nl/html/welkom.html.

A Systems Perspective: "Points to Consider"

Risk-Based Approaches That Focus Industry and Agency Attention on Critical Areas

Reduce Uncertainty to Enable Risk-Based Decisions; Critical Variables and Link to Clinical Relevance; Sources of Variability and "Risk to Quality": Currently a high degree of uncertainty with respect to critical variables, sources of variability and their clinical relevance delays approval of certain complex drug delivery systems (e.g., inhalation products). With increasing complexity in drugs and drug delivery systems this challenge is anticipated to increase and is likely to result in multiple review cycles for new drug applications and/or an inability to approve generic drug products in a timely manner.

Furthermore, significant industry and FDA resources are spent debating issues related to acceptable variability, need for additional in-process testing and how specification acceptance limits should be established. Often these debates are focused on acceptance limits or the statistical aspects. In these debates a proportionate focus on the underlying manufacturing science is often missing. For example;

- The protracted (about 10 years) debate on the issue of blend sampling and the relevance of in-process blend uniformity testing focused mainly on testing and statistics and did not fully leverage the manufacturing science aspect of the challenge. The PQRI proposal took a few steps in this direction (2, ACPS November 2001); today the full potential of a manufacturing science framework remains to be realized.
- For the last three years FDA and an industry group (IPAC-RS) have been debating a parametric tolerance interval test (PTIT) for delivered dose uniformity of inhalation products. The proposed PTIT approach has many desirable features including an approach to move away from the discrete/attribute criteria. However, uncertainties in what is "acceptable" variability have continued the debate for an extended period of time. Additionally, a focus on statistics alone has created a situation where the discussions have focused on "hypothesis testing" in routine production–i.e., testing to document quality instead of process control principles. The concept of "hypothesis testing" should essentially end at the process validation stage (2, ACPS October 2003).

Risk Communication: Knowledge Transfer and Management: A major element in risk management is risk communication. The challenge of risk communication between industry and FDA and within FDA should not be underestimated. It would be erroneous to assume that manufacturing

science can resolve all important risk to quality issues. Manufacturing science principles combined with effective risk management tools such as fault trees, failure mode effect analysis (FMEA) can provide a structure for risk-based decisions. Effective and efficient risk-decisions will require communication and collaboration between the CMC review and CGMP inspection functions, common data/knowledge bases, and a continuous learning and improvement approach.

Emerging Support Infrastructure for the "Desired State": Several academic institutions in the US, Europe, Switzerland, and Japan have incorporated PAT concepts in their curricula and several graduate students at these institutions are engaged in PAT research. Industry and academic collaborations (e.g., Consortium for Advanced Manufacturing of Pharmaceuticals or CAMP) are providing additional support.

In addition to numerous commercial vendors, several international scientific associations and societies have developed programs to support the "desired state." A few examples are provided below.

- The Royal Pharmaceutical Society's New Technology Forum (NTF) has continued its discussions on PAT with participation of FDA PAT Team members.

  Forum 5: Multivariate mathematical approaches.
  Forum 6: Rapid methods in microbiology.

- The Product Quality Research Institute Several ongoing and planned projects are focused on manufacturing science. The Manufacturing Technical Committee has been established and projects such as "Process Robustness of Oral Solid Dosage" are being developed (http://www.pqri.org). Several other PQRI projects (e.g., on excipients and dissolution testing) are essentially attempting to address common cause variability challenges in the current system.
  The ASTM E55 and other efforts such as NTF and PQRI are intended to be complementary in supporting PAT and the manufacturing science framework and to create a path to move efficiently towards the "desired state." The ASTM E55 focus on innovation should provide a "pull" on the "current state" to move it towards the "desired state" while the PQRI efforts provide the "push." The efforts of E55 on developing a standard for process understanding should provide a basis to ensure alignment of efforts and to create a synergistic "pull and push" vector in the direction of the "desired state."
- International Forum for Process Analytical Technology Manufacturer's Association (IFPATMA).
  http://www.ifpacma.org/ifpacMA-Benefits.html

IFPATMA is a not-for-profit consortium of manufacturers/suppliers dedicated to the advancement of quality systems for PAT in the pharmaceutical and related industries. The organization has a goal of standardization of practices for process analyzers and reducing the sensor qualification burden on pharmaceutical companies. Its efforts are aligned with ASTM E55 activities and with other organizations having similar goals.

- International Society of Pharmaceutical Engineering (ISPE) is developing a number of programs to support the "desired state" of pharmaceutical manufacturing. For example:
  - Discussions have been initiated to define the role and training needs of pharmaceutical engineering professionals.
  - A process equipment manufacturers' forum is under consideration to (a) enable and foster a risk-based approach to manufacturing and compliance, (b) accommodate new PAT technologies and implementation requirements, (c) speed the delivery of manufacturing capacity, and (d) improve quality while reducing costs, through a restructuring of current equipment qualification practices.
  - Creation of a peer-reviewed journal for science, engineering and Process Analytical Technology. The first issue is anticipated in January of 2006.
- American Association of Pharmaceutical Scientists (AAPS). AAPS conferences (e.g., the Arden House Conference) and workshops provided help in defining the "desired state." An AAPS PAT focus group has been established. http://www.aapspharmaceutica.com/inside/focus_groups/PAT/index.asp

Facilitate Industry Application of Modern Quality Management

"Out of the Corrective Action Crisis": Continuous Improvements: It can be argued that current low efficiency in pharmaceutical manufacturing is partly due to "self-imposed" constraints (e.g., approach to specifications based on discrete or the so called "zero tolerance" criteria, a less than optimal understanding of variability, etc.). This contributes towards keeping the current system in a corrective action mode. This approach also curtails our ability to prepare for future challenges.

Some would argue that corrective actions provide the necessary "constancy of purpose for improvement" and are necessary since manufacturing is a "step-child" of the industry because the difference between "cost of manufacturing" and the "price of drugs" is large. Keeping the system in

"corrective action mode" provides the leverage for ensuring improvements (i.e., to ensure the "current" in the CGMP's).

The argument has some validity, but it is based on an assumption that current practices (e.g., including measurement systems and product specifications) provide efficient means for identifying, understanding and then reducing variability (i.e., improvement). Quality assurance in the 21st century will need a sound basis for verifying such assumptions in the current system. To emphasize this point further, the case of dissolution test is cited again – the manner in which the current dissolution test is used provides good estimates of the mean dissolution profiles. However, in terms of variability (the dominant cause of OOS) the current approach to calibration and additional challenges in verifying certain inherent assumptions (e.g., relevance of hydrodynamic variability) makes it difficult for a commercial manufacturer to verify inherent assumptions and to document lower variability than the USP calibrator tablets. Therefore, without the ability to understand and document variability reduction (improvement) the "corrective action mode" may not be able to facilitate improvement in many situations. There are other undesirable consequences, such as:

- A constant "corrective action mode" amounts to "crying wolf" on a very frequent basis thus making the system less responsive to situations when a "real wolf" appears.
- This mode produces anxiety, fear, and disincentives to improvement among the production staff. This can set up an environment of high risk to quality and safety. Some aspects of this are further illustrated in section "Drive cut fear' that inhibits continuous. Learning curd improvement, and that which can increase risk".

Science-Based Regulatory Flexibility for Continuous Improvements: The concept of continuous improvement has a long history and a well founded structure and format as exemplified by the Evolutionary Operations or EVOP (5) and the "Kizen" principles. Kizen (*Ky' zen)* is a Japanese word introduced in the West (~late 70's) and translated as "Continuous Improvement"—slow, incremental, but constant.

The basic philosophy of EVOP is that "it is inefficient to run an industrial process in such a way that only a product is produced, and that a process should be operated so as to produce not only a product but also information on how to improve the product." Effective knowledge transfer and communication between organizations is essential for continuous improvement; equally important is a system to collect and analyze information throughout a product's life cycle. Such a system can assist in identifying and addressing sources of variability and sharing this information with all organizations (e.g., development, regulatory, etc.).

In the current system the "fear" of finding a ("new") source of variability inhibits information collection on commercial products beyond the batch records. Although the PAT Guidance provides a regulatory mechanism to address this issue by clarifying that additional information is research data, it is limited to PAT applications. The concept of continued learning in the production setting should be encouraged in the entire regulatory system.

"Drive Out Fear" That Inhibits Continuous Learning and Improvement, and That Which Can Increase Risk: It is important to appreciate that there are many dimensions to the challenge of "fear." For those who may engage in amoral or unethical behaviour, the regulatory "fear" is a desirable deterrent. Quality by design and process understanding aspects of manufacturing science provide the regulatory system with additional means to address many of the "undesirable" and "desirable" dimensions of "fear."

- Fear is contradictory to continuous improvement and a broad regulatory approach is needed to address this challenge. Timely risk assessment, communication, information, and collaboration between CMC review and CGMP inspection functions will be essential components of such a regulatory approach. In addition, common data bases and information systems will be necessary.
- A combination of "fear" (of failure) and insufficient process understanding can create situations that can increase risk. The following example illustrates this point.
    - The Warning Letter citation below may be an example of a poorly understood process since OOS investigations were unable to determine the root cause(s) of the problem. In order to conform to in-process blend uniformity test specifications, powder blends were either enriched with additional drug or diluted with other ingredients. In an essentially closed system (blender) this is an unacceptable practice (a violation of "*Do what you say"*) and can pose significant risk to patients.
    - The example emphasizes that process understanding and quality by design principles offer a more attractive means to mitigate risks posed in the following:

PRODUCTION SYSTEM

4. Deviations from approved drug formulations are performed when in-process specifications are not met. The deviations consist of adding varying quantities of active ingredient or diluting the batch. There are no validation studies to assure that there is no adverse product impact throughout shelf life. Investigations do

not always determine the cause of the abnormal assay result or corrective/preventive action. For example:

a. In-process assay of XXXXX revealed low potency results ranging from XXXXX (specifications are XXXXX. An additional quantity of XXXXX of the active ingredients was added to the batch. There is no determination into the cause of the low assay or preventative actions from recurrence.

"Pride of Workmanship" and Continuous Learning: Frequent corrective actions take away the "pride of workmanship" from production operators and other staff in industrial operations. In addition, FDA's penalty system (e.g., Warning Letters) is often construed to be directed at industrial operations. The ability to distinguish between common cause and special cause variability can be an important element in the FDA's penalty system and facilitate a move towards a continuous improvement approach and help build/improve the "pride of workmanship" dimension.

Enhanced Quality Systems Approaches into the Agency's Business processes

PAT Team Approach to CMC Review and CGMP Inspections: The value and advantages of a team approach to CMC review and CGMP inspections has been recognized and practiced for many years (e.g., Team Bio). This principle was utilized to develop the PAT Team. However, to accommodate specific objectives of the initiative and the need for a systems approach in the PAT Team, a joint training and certification process with team building was developed. The entire team of CMC reviewers, CGMP investigators, and compliance officers trained together on all aspects of PAT.

To ensure that this team concept is "institutionalized" and for its continuous improvement, the PAT Team process will be under the FDA's Quality Systems Framework. This should also help in ensuring quality and consistency of reviews, inspections, and other regulatory activities.

Manufacturing Science Foundation of the FDA's Quality System: The number of "quality movement" or trends in the 20th Century (1950s-Sampling plans; 1960s Zero-Defect Movement; 1980s - ISO-9000 & Malcolm Baldrige Award; 1990s - QS-9000, Total Quality Management, Six Sigma, etc) can create a perception that these trends are "lurching from fad to fad" or suggest that these trends represent continuous improvement towards an ideal quality system (22). An element that is essential to recognize is that of process understanding; without process understanding, the effectiveness of any quality system will be limited and without a sound manufacturing science foundation, a pharmaceutical quality system will fail to realize its full potential. A quality system should provide a sound

framework for the transfer of process knowledge from development to the commercial manufacturing processes and for post development changes and optimization (23).

Continuous Improvement—Change Control and Life Cycle Management: A flexible, science and risk-based approach to post approval changes will be essential to facilitate continuous improvement. Regulatory mechanisms for ''life cycle management'' are necessary. ''Change Control'' is a well-known CGMP regulatory concept that focuses on managing change to prevent unintended consequences and this can be a path towards continuous improvement. In this regard, *change* towards continuous improvement should be encouraged. This means a manufacturer is empowered to make changes based on the variability of materials used in manufacturing and optimization of the process from learning over time (23); therefore, a company's quality system should consider this opportunity. Regulatory management of a flexible ''change control'' process will require a team approach to CMC review and CGMP inspections, in many ways similar to the PAT team process.

''Pride of Workmanship'' and ''Continuous Learning'': Pride of workmanship of FDA staff should be an essential element of the FDA's Quality System. Manufacturing science and PAT training and professional development opportunities should provide a means for FDA staff to be recognized as leaders in a number of scientific and technical areas. Continuing education and training programs should therefore be supported and be a part of the quality system. The concept of ''peer review'' should be considered and mechanisms developed to recognize scientific and regulatory contributions that help the pharmaceutical community move towards the ''desired state.''

Break Down Organizational Barriers: Success of the CGMP Initiative depends on a team approach to pharmaceutical quality. Lessons learned from the PAT team building activities suggest that organizational barriers can be removed through open dialogue and opportunities to engage in activities that relate to areas of common interests. The manufacturing science vocabulary and systems thinking it induces can also facilitate international discussions (e.g., in ICH and PIC/S) and cooperation.

Collaborations and Recommendations

Team BIO and PAT Team

During the course of the CGMP Initiative the PAT team was developed and implemented through collaboration between ORA, CVM and CDER. The Office of Biotechnology moved into CDER towards the end of the PAT training process. The final guidance extends the PAT framework to CDER's Office of Biotechnology (OBP). PAT applications will be managed through

collaborations with the PAT Team. A second PAT team is planned and will include CDER's Office of Biotechnology, Office of Compliance and ORA Team-Bio representatives. Formation of the second PAT Team will provide an additional opportunity to develop close collaboration and cooperation between the PAT team and Team-Bio. This opportunity should be utilized to identify best practices and to develop recommendations for a broader team approach.

ICH Q9 & Risk Based Site Selection Model for CGMP Inspections

A structured regulatory format for risk assessment and management will be essential for moving towards the "desired state." The PAT framework and ICH Q8 will provide a basis for risk mitigation. Risk management principles and tools will be necessary to describe and communicate the level of risk-mitigation achieved through quality by design and process understanding. Therefore, the principles and tools for risk management and communication currently being developed in ICH Q9 and the emerging risk based site selection model for CGMP inspections should connect well with the manufacturing science and the PAT framework to ensure:

- *Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability.*
- *Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.*

Changes Without Prior Review: Draft Guidance, Comparability Protocol

A flexible, science and risk-based approach to *post approval changes* will be essential to facilitate continuous improvement. The new compliance policy guide CPG 7132c.08 recognizes the role of emerging advanced engineering principles and control technologies in ensuring batch quality (24). For drugs produced using these new principles and technologies, this CPG provides for possible exceptions to the need for manufacturing multiple conformance batches prior to initial marketing. This version also deletes the previous reference to "three" validation (or conformance) batches at commercial scale as adequate minimum proof of process validity—a number is no longer suggested. This is a major step forward in facilitating continuous improvement.

As discussed in section "Continuous Improvement—Change Control and Life Cycle Management." *Change* towards continuous improvement should be encouraged. Quality by design and process understanding can

provide a basis to allow those manufacturer that have demonstrated adequate level of process understanding to make *changes without prior review* within the "change control" provisions of their quality system under the CGMP inspectional oversight.

Although progress on ICH Q8 has been significant, additional work is necessary to articulate the relationship between "*adequate level of process understanding and regulatory flexibility to make changes without prior review*." At the recommendations of the ACPS Manufacturing Subcommittee (July 2004) a working group will be assembled to develop illustrative case examples. ICH Q8 and illustrative examples should then be a basis to further improve the draft comparability guidance to facilitate continuous improvements.

Proposed ICH Q10

Life cycle management and change control provide a mechanism for continuous improvement. To support continuous improvement through change control a quality system would need to be based on principles of manufacturing science and risk-management. The proposed ICH Q10 guidance is an opportunity to accomplish this task.

Product Specialists on Inspections and Pharmaceutical Inspectorate

The PAT team building and training program identified several challenges, of these the most critical challenge was of that of organizational barrier (review–compliance-inspections). An independent contractor was asked to apply principles of organizational engineering to understand different perspectives and based on this information, team building programs and joint training programs were developed.

Team building exercises and joint training programs were critical for overcoming the organizational barriers and communication challenges. It is recommended that similar team building and training opportunities be created for CMC reviewers, compliance officers and the Pharmaceutical Inspectorate. Lessons learned from the PAT Team and Team-Bio should also be utilized to support the "Product Specialists on Inspection" program.

Next Steps and Considerations for the Critical Path Initiative

PAT

The PAT process has been successful in bringing a systems perspective and a team approach to facilitate innovation. The PAT team has approved one application that included a joint team inspection and has recently completed a pre-operational visit for a major PAT application. Several PAT proposals

have been received and it is expected that many of these will be received as applications in the near future. The next steps in the PAT process include:

- International scientific workshop on the PAT Guidance in the United States, Europe and Japan
- Incorporation of the PAT process under the FDA's Quality System
- Continued participation in ASTM E55 Committee to support development of standards consistent with the PAT framework
- CBER and Team-Bio representative to join PAT Steering Committee
- Selection of the second PAT Team (to include Office of Biotechnology, Compliance and ORA Team-Bio CGMP Inspection staff)
- Teambuilding, training and certification of the second team
- Extend invitations to Health Canada, MHLW, and EMEA to participate in the second training program
- Share lessons learned and training materials with Health Canada, MHLW, and EMEA
- Continuing education for the current PAT team
- PAT Team and Team-Bio collaboration to identify best practices and lessons learned; recommendations on how to develop a team approach between "Product Specialists" and Pharmaceutical Inspectorate
- Critical Path Research and research collaborations (academia and industry)
- Strengthen the emerging support structure in scientific societies and association (e.g., AAPS, ISPE, IFPATMA, PDA, and others)
- Following the second PAT team training, expand the PAT program to include all *Product Specialist* and *Pharmaceutical Inspectorate*

Manufacturing Science

ICH Q8 will describe the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. It is not intended to be a "how to" guidance. It will provide sponsors of drug applications an opportunity to present knowledge gained during development of a product and its manufacturing process and relevant prior knowledge. It will indicate areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches to support continuous improvement.

- The FDA's goal at the next ICH meeting (November 2004, Japan) is to articulate and build consensus on a description of how a greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches needed to support continuous improvement.

  - If this is agreed upon in November 2004, ICH Q8 would reach Step 2 and be available for public comment.
  - It should be recognized that each section within "State-of-the-Art Pharmaceutical Science" P.2 Pharmaceutical Development section will impact the other P2 sections and similarly other sections of a submission and the CGMP's inspection process. By recognizing this as a complex design system that involves multiple attributes, goals, constraints, multidisciplinary design teams (subsystems), different degrees of uncertainty, risk tolerance, etc., we may find opportunities to develop robust designs and design space that provides a sound basis for risk assessment and mitigation.

- Although to a large degree consensus has been established on the "desired state" it should be noted that there is often a tendency for a consensus on collective ends to attenuate when specifics are addressed. This is often due to divergent understanding of the problem being addressed and/or differences in interests and/or issues in representation of the problem being addressed. It is hoped that this report will help in further consolidating and strengthening the consensus for moving towards the "desired state"
- Under the ACPS Manufacturing Subcommittee a working group will be formed to identify specific steps needed to move towards the desired state. The group will also develop illustrative case studies to support the ICH Q8 document and CPG 7132c.08
- ACPS recommendations on regulatory flexibility for post approval changes (e.g., reduce the need for prior review) will be considered for improving the draft Comparability Protocol Guidance (for small molecules only).
- A combination of the PAT Guidance, CPG 7132c.08, modified draft Comparability Protocol Guidance (for small molecules only) along with other work products of the CGMP Initiative are expected to facilitate a move towards the desired state. The proposed ICH Q10 will need to consider these concepts and policies and provide additional guidance on quality systems for change control to facilitate continuous improvement.

The effectiveness of the regulatory framework for innovation (PAT Guidance) and manufacturing science (emerging ICH Q8) when implemented should be evaluated periodically to guide continuous improvement. Objective metrics will need to be developed to measure the level of systems thinking achieved in the application of manufacturing science principles and opportunities realized within the agency, by the industry, and the larger pharmaceutical community. It is expected that a continuous improvement plan will be developed for both PAT and ICH Q8 under the FDA's Quality System.

Critical Path Initiative (25)

In the short duration of the CGMP Initiative significant progress was made articulating, building consensus on, the "desired state" for pharmaceutical manufacturing, and developing a regulatory framework for innovation and continuous improvement. Some have characterized this progress as "revolutionary" (10). From the PAT Team and Manufacturing Science Working Group perspective the progress made to date was because we worked as team to identify and realize opportunities to improve our ability to meet our public health objectives.

Significant challenges lie ahead for the pharmaceutical community and for regulators to move to the "desired state" for pharmaceutical manufacturing in the 21st century. Nevertheless, important steps have already been taken. In addition, some of these challenges can be addressed through the FDA's Critical Path Initiative.

- The Executive Order 13329 Encouraging Innovation in Manufacturing (February 2004) recognizes that "*Continued technological innovation is critical to a strong manufacturing sector in the United States economy. The Federal Government has an important role, through the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) programs, in helping to advance innovation, including innovation in manufacturing, through small businesses.*" *http://www.sba.gov/SBIR/execorder.html*
    - This provides an opportunity for FDA to support innovation by collaborating with other federal agencies to identify priority for pharmaceutical manufacturing-related research and development.
- The team approach and systems perspective under the CGMP Initiative only addressed a part of the pharmaceutical system. Quality by design and process understanding to a large extent is achieved in a research and development organization; ICH Q8 is the bridge between the CGMP Initiative and the rest of the regulatory system.
    - Pharmaceutical product development is a complex and creative design process that involves many factors, many unknowns, many disciplines, many decision-makers, and has multiple iterations and a long life-cycle. Significant uncertainty is created when a particular disciplinary design team must try to connect their subsystem to another disciplinary subsystem (e.g., Clinical-CMC-CGMP). Each subsystem can have its own goals and constraints that must be satisfied along with the system-level goals and constraints. It is possible that goals of one subsystem may not necessarily be satisfactory from the view of another

subsystem and design variables in one subsystem may be controlled by other disciplinary subsystems.
    - Development of systematic regulatory framework based on complexity and scientific uncertainty should facilitate all three dimensions of the critical path. Such a system will also need to consider the multidisciplinary communication challenges in product development.
- The scientific and technical challenges on the critical path towards the "desired state" are significant. The traditional empirical approaches will need to be replaced with a much more fundamental scientific understanding (26,27). This will require the talent and know-how of many scientific and technical disciplines. Without sufficient and sustained support our Nation's pharmaceutical education and research system will be unable to meet the needs of the desired state. Significant collaboration and cooperation among industry, academia, and public agencies (e.g., National Science Foundation and National Institutes of Health) including FDA will be necessary to find solutions to this challenge.

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Both pure and applied science have gradually pushed further and further the requirements for accuracy and precision. However, applied science, particularly in the mass production of interchangeable parts, is even more exacting than pure science in certain matters of accuracy and precision. Walter A. Shewhart.

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